A feasibility study of paired Continuous Glucose Monitoring (CGM) intra-partum and in the newborn in pregnancies complicated by Type 1 Diabetes

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Key words: Type 1 Diabetes, neonatal, perinatal, glucose, hyperglycaemia, hypoglycaemia

Running title: CGM in T1D mother-infant pairs

Word count: abstract n=250, manuscript n=2544

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Funding: The neonatal CGM was funded by a Diabetes Wellness and Research Foundation (DRWF) project grant. The CONCEPTT trial was funded by Juvenile Diabetes Research Foundation, Canadian Clinical Trials Network, and the National Institute for Health Research (HRM Career Development Fellowship, CDF-2013-06-035).

Abstract

Aim: To describe the continuous glucose monitoring (CGM) profiles of type 1 diabetes (T1D) offspring in the early neonatal period and its association with maternal intrapartum glucose control.

Methods: A prospective observational study of T1D pregnant women and their neonatal offspring. Women had a CGM sensor inserted 2-3 days prior to delivery. Infants had a masked CGM sensor inserted as soon as possible following delivery. Maternal glycaemic outcomes were time-in-target (70-140 mg/dL [3.9-7.8 mmol/L]), hyperglycaemia >140 mg/dL (7.8 mmol/L) and mean CGM glucose during the 24 hours preceding delivery. Neonatal outcomes included lowest recorded blood glucose concentration, and CGM measures (glucose <47 mg/dL [2.6 mmol/L], time-in-target (47-144 mg/dL [2.6-8.0 mmol/L]), glucose SD) during the first 72 hours of life.

Results: Data were available for 16 mother-infant pairs. Mothers had a mean age (SD) 32.3 (4.3) years, T1D duration 17.6 (6.8) years, first antenatal HbA1c 7.4 (0.8)% (57 [8.5] mmol/mol). In the 24 hours preceding delivery, mothers spent mean (SD) 72 (20) % time-in-target (70-140 mg/dL [3.9-7.8 mmol/L]), 19 (15) % time >140 mg/dL (7.8 mmol/L), and 9 (9) % time < 70 mg/dL (3.9 mmol/L) with mean (SD) CGM glucose 113 (9) mg/dL (6.3 [0.7] mmol/L). 15 infants (93.8%) had ≥1 blood glucose concentration < 47 mg/dL (2.6 mmol/L) and five had ≥1 blood glucose concentration < 18 mg/dL (1.0 mmol/L). The mean infant CGM glucose on days 1, 2, and 3 of life was 63 (14), 67 (13), 76 (11) mg/dL (3.5 [0.8], 3.7 [0.7], and 4.2 [0.6] mmol/L). Four infants (25%) spent more than 50% time with CGM glucose levels < 47 mg/dL (2.6 mmol/L) on day 1.

Conclusions: CGM detected widespread neonatal hypoglycaemia, even among mothers with good intrapartum glucose control. .

Introduction

Infants of mothers with type 1 diabetes (T1D) are at increased risk of complications, of which neonatal hypoglycaemia, is the most common neonatal concern. Approximately two in three infants born following a pregnancy complicated by T1D have neonatal hypoglycaemia, and 30-40% require admission to neonatal intensive care units (NICU) (1,2). National audit data from England and Wales have highlighted the high prevalence of hypoglycaemia as a cause of term admissions and made it a priority target in trying to reduce term admissions and keep mothers and their babies together (3).

While neonatal hypoglycaemia is often asymptomatic, it can also have long-term consequences including neurocognitive impairment and lower academic achievement (4–6). A population-based study of 1395 children found that even transient newborn hypoglycaemia (a single blood glucose measurement < 34, 40, or 44 mg/dL [1.9, 2.2, or 2.5 mmol/L]) was associated with lower probability of literacy and mathematics proficiency in fourth-grade tests (6). Additionally, a recent study of infants identified to be at risk of neonatal hypoglycaemia, showed that those with hypoglycaemia, detected clinically with routine glucose monitoring and/or asymptomatic episodes detected with CGM, had a 3-4-fold increased risk of low executive function at 4.5 years of age (7).

Although neonatal hypoglycaemia is reported to be more common in infants of T1D mothers with poorer antenatal and intrapartum glycaemic control (8,9) this relationship is inconsistently observed (10–16). The timing of the relationship is also poorly understood. Randomised trial data confirm that CGM improves maternal antenatal glycaemic control and neonatal health outcomes, with the CONCEPTT trial having described a halving in the odds ratio for neonatal hypoglycaemia (1). However, it is unclear whether the reduction in neonatal hypoglycaemia

and in NICU admissions was solely attributed to maternal antenatal glycaemia or whether intrapartum glycaemia during labour and delivery also contributed.

There remains controversy as to the optimal screening strategy and diagnostic thresholds for detection and management of neonatal hypoglycaemia (17–20). CGM has the potential to inform optimal management of glucose dysregulation in the neonatal period (21) but CGM data in T1D offspring are limited, particularly in the first 24-72 hours of life. The aim of this study was to explore the feasibility of using CGM to describe the CGM glucose profiles of type 1 diabetes (T1D) offspring in the early neonatal period. A secondary objective was to investigate the relationship between maternal intrapartum and neonatal post-partum glucose control in T1D pregnancy.

Research Design and Methods

Maternal participants

Pregnant CGM users were approached about potential participation in the study during their third trimester. Those who wished to participate provided informed consent for themselves and assent for their neonate, with parental written consent for neonates confirmed within 24 hours of delivery. Inclusion criteria included maternal familiarity with masked or real-time CGM, intensive insulin therapy using either multiple daily injections of insulin (MDI) or insulin pump therapy, and singleton pregnancy. Exclusion criteria included known congenital anomaly or neonates with severe respiratory distress.

Pregnant women with T1D had a CGM sensor inserted 2-3 days prior to anticipated delivery. Participants already using the Guardian® REAL-Time or MiniMed Minilink® CGM (both Medtronic, Northridge, CA) continued their usual CGM. Participants using the Freestyle Navigator II (Abbott Diabetes Care) were fitted with an additional masked CGM sensor for

measurements used in this study (iPro™ 2 Professional CGM, Medtronic, Northridge, CA, USA). Participants were asked to measure capillary glucose concentration using their routine glucometer and to record at least 4 daily readings.

Neonatal participants

As soon as possible following delivery (aiming for within 4 hours), an appropriately trained member of the research team fitted the newborn infant with a masked CGM device (iPro™2 Professional CGM, Medtronic, Northridge, CA, USA). The sensors were inserted into the lateral aspect of the infant's thigh. While infants had the sensor in situ, their routine blood glucose monitoring samples were used to calibrate the CGM. Concurrent sampling was performed for measurement of infant blood ketones. There were no additional blood glucose samples taken from infants as a result of this study.

Study design

A prospective observational study of pregnant women with T1D and their neonatal offspring. All infant CGM data were masked and therefore not available to parents, clinicians, or researchers. Infants otherwise received standard neonatal clinical care. Standard neonatal care required that all T1D offspring were screened for hypoglycaemia, clinically defined as blood glucose concentration <47 mg/dL (2.6 mmol/L). A standard treatment protocol was used for blood glucose concentration <47 mg/dL (2.6 mmol/L). Buccal dextrose gel was not used during this study. All infants required three pre-feed blood glucose levels >47 mg/dL (2.6 mmol/L) prior to hospital discharge. The CGM sensor remained in situ until the infant was ready for hospital discharge, for up to a maximum of seven days duration.

Outcomes

Maternal and neonatal demographics details were obtained from the medical records, including gestational age at delivery, birthweight, need for supplemental feeds, intravenous dextrose infusion or NICU admission. Maternal glycaemic outcomes included percentage time-in-target range (70-140 mg/dL [3.9-7.8 mmol/L]), hyperglycaemia >140 mg/dL (7.8 mmol/L) and mean CGM glucose concentration during the 24 hours preceding delivery. Neonatal outcomes included the lowest recorded blood glucose concentration (measured on either blood gas (Cobas b 221, Roche Diagnostics Limited, UK), or point of care meters (Nova StatStrip® meters, Novabiomedical MA, USA)), percentage time with sensor glucose concentration <47 mg/dL (2.6 mmol/L), percentage time-in-target range (sensor glucose 47-144 mg/dL [2.6-8.0 mmol/L]) and standard deviation (SD) of sensor glucose within the first 48 hours of life. The clinical study protocol was approved by the Health Research Authority, East of England Regional Ethics Committee (14/EE/0001).

Statistical analysis

Glucose outcomes were calculated with GStat Version 2.2 software (University of Cambridge, Cambridge UK). Statistical analyses were conducted using SPSS, R and Stata version 14.1. The percentage of time-in-target range, time hypoglycaemic and time hyperglycaemic were summarised as means (standard deviation) or medians (IQR) where appropriate. Student's t-tests and Mann Whitney Wilcoxon tests were performed as appropriate, and presented with p values and/or 95% confidence intervals. A p value of <0.05 was considered significant.

Results

Twenty-two pregnant women with T1D were recruited, 21 participants had both maternal and infant CGM sensors applied (one pair could not be included because there was insufficient CGM equipment available at the time of delivery). The CGM sensor failed to collect any data from five infants. CGM data were therefore available for 16 mother-infant pairs.

Mothers had a mean age (SD) of 32.3 (4.3) years, T1D duration of 17.6 (6.8) years, first antenatal HbA1c 7.4 (0.8)% (57 [8.5] mmol/mol), and BMI of 26.1 (4.1) kg/m^2. Eight mothers (50%) used insulin pump therapy, four (25%) used MDI and four (25%) used hybrid closed-loop insulin delivery systems. Full details of the baseline maternal characteristics are provided (See Table S1, online supplement).

Maternal glycaemia

In the 24 hours prior to infant delivery, mothers spent a mean (SD) of 72 (20) % time (17.3 hours/day) within target range (70-140 mg/dL [3.9-7.8 mmol/L]), 19 (15) % time (4.6 hours/day) >140 mg/dL (7.8 mmol/L), and 9 (9) % time (2.2 hours/day) <70 mg/dL (3.9 mmol/L) (Table 1). Their mean (SD) sensor glucose was 113 (13) mg/dL (6.3 [0.7] mmol/L). There were no significant differences in percentage time-in-target or mean CGM glucose between mothers treated with insulin pump, MDI, or closed-loop (CL): (mean [SD] time-in-target 66.0 [22.1]% pump, 77.0 [20.1]% MDI, 78.5 [13.4]% CL, p=0.51; mean [SD] glucose 113 [16] mg/dL (6.3 [0.9] mmol/L) pump, 112 [16] mg/dL (6.2 [0.9] mmol/L) MDI, 115 [2] mg/dL (6.4 [0.1] mmol/L) CL, p=0.94). There was however substantial intra-individual variability in maternal glucose control (Table 1).

Obstetric and neonatal outcomes

Infants were delivered at a mean of 37+2 weeks' gestation. Two had vaginal deliveries and 14 delivered via caesarean section (9 elective, 5 emergency). Infant birthweight ranged from 2810

to 4675 g (mean [SD] 3887 [519] g). Six infants (37.5%) weighed greater than 4000g, and two (12.5%) weighed greater than 4500g (See Table S2, online supplement). Six infants (37.5%) had a sex and gestational age-specific birthweight centile greater than 90th percentile.

Neonatal glycaemia

Fifteen newborns (93.8%) had at least one blood glucose concentration <47 mg/dL (2.6 mmol/L). The lowest recorded blood glucose concentrations ranged from 13 mg/dL (0.7 mmol/L) to 61 mg/dL (3.4 mmol/L), with a mean (SD) of 31 (14) mg/dL (1.7 [0.8] mmol/L) (Table 2). There was no correlation between lowest recorded blood glucose concentration and maternal mean glucose, time-in-target, or hyperglycaemia in the 24 hours prior to delivery (R^2 = 0.007, p = 0.77 for mean CGM glucose, R^2 = 0.03, p = 0.52 for time-in-target, R^2 = 0.003, p = 0.85 for hyperglycaemia).

For the newborn infants on days 1, 2, and 3 of life the mean (SD) CGM glucose was 63 (14) mg/dL (3.5 [0.8] mmol/L), 67 [13] mg/dL (3.7 [0.7] mmol/L), and 76 [11] mg/dL (4.2 [0.6] mmol/L) respectively. The percentage of time infants spent with CGM glucose levels < 47 mg/dL (2.6 mmol/L) varied from 0-100% on day 1, 0-57% on day 2, and 0-21% on day 3 of life (median [IQR] for day 1 = 0 [0, 12.8]%, day 2 = 0 [0, 0.5], day 3 = 0 [0, 6.0]). Four infants (25%) spent more than 50% of the time with CGM glucose levels < 47 mg/dL (2.6 mmol/L) in the first 24 hours. Three of these four infants were not treated with IV dextrose. Two of the three infants who had persistent hypoglycaemia on day 3 were also not treated with IV dextrose but remained only enterally fed.

All infants were given supplementary feeds with either expressed breast milk or infant formula. Additionally, 10 infants (62.5%) received treatment with intravenous dextrose. Of the 10

infants who had blood ketones measured, only one had a detectable ketone concentration at any time (4 mg/dL [0.2 mmol/L]). All other ketone measurements were <12 mg/dL (0.1 mmol/L).

The median (IQR) mean absolute relative difference (MARD) between CGM and glucometer readings was 9.7 (7.4, 12.6) %.

Across the 16 infants, there were 51 time-matched sensor and blood glucose results <63 mg/dL mmol/L and 21 time-matched values <50 mg/dL. The MARD was 9.1 (3.6, 16.4)% for values <63 mg/dL, and 9.1 (4.5 16.7)% for values <50 mg/dL. The mean absolute difference (MAD) was 5 mg/dL for values <63 mg/dL and 4 mg/dL for values <50 mg/dL.

Infants treated with IV dextrose

Although the mothers of infants not treated with IV dextrose had lower mean glucose, higher time-in-target and less hyperglycaemia, these differences did not reach statistical significance (Table 3). Infants treated with IV dextrose had a mean CGM glucose level 18 mg/dL (1.0 mmol/L) higher in the first 24 hours of life than those who did not receive treatment with IV dextrose (p = 0.006; Table 3). The mean CGM glucose in IV dextrose treated infants also remained higher on day 2 compared with infants not treated with dextrose (mean [SD] sensor glucose 72 [13] mg/dL [4.0 (0.7) mmol/L] vs 58 [7] mg/dL [3.2 (0.4) mmol/L], p = 0.03). There was no different in rates of IV dextrose administration according to mode of delivery (6 of 9 who delivered via elective caesarean section had IV treatment vs 3 of 7 in those who delivered via emergency caesarean section or vaginal delivery; $p = 0.61$).

Infants with blood glucose concentration < 18 mg/dL (1.0 mmol/L)

Although infants whose blood glucose did not drop to ≤ 18 mg/dL (1.0 mmol/L) appeared to have mothers with better glucose control (lower mean glucose, higher time-in-target, less glucose variability, lower HbA1c in all trimesters) these differences did not reach statistical significance. Infants with at least one recorded blood glucose ≤ 18 mg/dL (1.0 mmol/L) were born an average of 1.5 weeks earlier than those who did not drop to ≤ 18 mg/dL (1.0 mmol/L) (p = 0.01; Table 4). Infants delivered via elective section were more likely to have at least one glucose value ≤ 1.0 mmol/L than those delivered by emergency section or vaginally (5 of 9 in those who delivered by elective caesarean section vs 0 of 7 who delivered by emergency caesarean section or vaginal delivery; $p = 0.03$).

Discussion

In our study, neonatal hypoglycaemia was near-universal with 15 of 16 infants having at least one blood glucose measurement < 47 mg/dL (2.6 mmol/L) and five having at least one measurement ≤ 18 mg/dL (1.0 mmol/L). Ten neonates were treated with intravenous dextrose, and they had a mean glucose that was 18 mg/dL (1.0 mmol/L) higher than untreated infants. A surprising and unexpected finding was that the infants with the most prolonged exposure to hypoglycaemia were those who were managed on the routine postnatal ward.

While some studies have found neonatal hypoglycaemia to be associated with maternal intrapartum glucose control (13,14,22–24), these data are inconsistent (25), and the pathogenesis of neonatal hypoglycaemia remains poorly understood. It is well established that preterm delivery and large for gestational age are important contributors to hypoglycaemia in T1D offspring, and indeed we found that infants who had at least 1 glucose measurement below 18 mg/dL (1.0 mmol/L) were larger, and born earlier. While prematurity itself is a risk factor for hypoglycaemia, in our study the explanation for this finding is less clear. The group of infants with glucose values ≤ 18mg/dL (1.0 mmol/L) may represent a cohort whose mothers

had poorer glycaemic control (as suggested by trends in HbA1c throughout pregnancy) and these women are more likely to be induced early due to obstetric complications. Infants born earlier also tended to be larger (median birthweight centile >99 for infants born at or before 37 weeks vs 93 for those born after 37 weeks gestation), perhaps because of poorer maternal glycaemic control, which may mean that these infants were more likely to be hyperinsulinaemic and therefore have lower blood glucose levels.

Our results are consistent with data suggesting that increasing maternal hyperglycaemia is associated with neonatal hypoglycaemia, although with small numbers the differences in the proportion of CGM time spent above and within target range were not statistically significant. Larger adequately powered studies of maternal intra-partum glucose control are required to understand the contribution of maternal intrapartum hyperglycaemia to neonatal hypoglycemia.

Our study also demonstrated that four infants spent more than half of their first day of life with CGM glucose levels < 47 mg/dL (2.6 mmol/L). This may be clinically important because even a single low glucose measurement has been associated with lower test proficiency achievement at 10 years of age (6). Furthermore CGM detected hypoglycaemia is associated with lower executive functioning in pre-school aged children (7). While routine clinical blood glucose monitoring did demonstrate some level of hypoglycaemia, it did not reveal the severity or duration of hypoglycaemia exposure and three of these were treated only with supplementary feeds. These data are consistent with those of Harris et al (26), who also found that CGM detected greater exposure to hypoglycaemia than standard newborn heel-prick monitoring.

Little is known about what represents normoglycaemia in the early neonatal period either in terms of target glucose levels or glucose fluctuations, in infants of women with diabetes or

healthy newborns (17,18). In utero, glucose concentrations are normally maintained between 72-108 mg/dL (4-6 mmol/L) (27). It is reported that neonatal glucose concentrations fall after birth, reaching a nadir at approximately one-to-two hours after delivery, depending on gestational age and other factors (28,29). Recent studies in healthy term infants suggest that mean glucose remains steady at approximately 54 mg/dL (3.0 mmol/L) during the first two days of life, before gradually increasing to approximately 72 mg/dL (4.0 mmol/L) thereafter (30–32). The mean glucose of 52 mg/dL (2.9 mmol/L) in infants treated with supplementary feeds is similar to that described in other newborn cohorts having glucose levels measured due to an anticipated risk of perinatal hypoglycaemia (32,33). However, clinical concerns remain in T1D offspring due to the potential impact of higher neonatal insulin levels suppressing the availability of alternative fuels.

Those infants treated with IV dextrose had a mean CGM glucose concentration approximately 18 mg/dL (1.0 mmol/L) higher than the infants in our study who did not receive IV dextrose. Whether this is beneficial or represents overtreatment remains unclear. Further studies are required to better understand the role of alternative fuels, as well as glycaemic exposure on longer term outcomes. The landmark trial of neonatal hypoglycaemia and neurocognitive outcomes by McKinlay et al included 28 mothers with pregestational diabetes, among whom 20/28 (71%) newborns experienced hypoglycaemia (7). The data from this trial suggests a U-shaped relationship between neonatal glucose and subsequent poor neurocognitive outcomes. They also highlighted increased risk of neurosensory impairment in infants with neonatal hypoglycaemia followed by higher glucose levels in the first 48-hours.

Other neonatal CGM studies were performed on preterm infants without maternal CGM (21), or which included offspring of mothers with diabetes, either did not specify the diabetes type

(34) or included only small numbers of T1D offspring (n=3) (35). These studies did not include details of maternal glucose control and did not specify the timing of CGM initiation.

To our knowledge, ours is the first study to perform CGM both on women with T1D and on their infants. The masked CGM in the early neonatal period provided data under standard clinical conditions. We included a varied population of women, including mothers with long duration of T1D with a range of glycaemic control and using a variety of insulin delivery methods. We made every effort to insert the CGM sensor as soon as possible in the first 4 hours of life. We also included infants on routine postnatal wards in addition to those in the NICU.

This study also has limitations. Standard neonatal care required screening for hypoglycaemia and clinical interventions will have impacted on neonatal glucose control. Other limitations include accuracy of CGM at low glucose levels and the fact that CGM is not designed for use in the early neonatal period. The sensors were inserted manually and use calibration algorithms designed for older children with higher glucose concentrations (36). Our study was not designed to assess accuracy of the CGM system used, and blood glucose measurements were performed as clinically indicated rather than at specific times or glucose thresholds (given CGM data were masked to investigators and clinicians) and so accuracy results must be interpreted with caution. However, we found a median MAD of 9.7% between the CGM and glucometer readings overall, and 9.1% at values <63 mg/dL, suggesting acceptable accuracy (37). This is consistent with previous studies of similar systems in infant populations, which also demonstrated acceptable accuracy using the same sensor as our study with a different monitor (38), and using an older Medtronic sensor (39). The latter study found that this older CGM system was less accurate at lower glucose levels, when more than 50% of readings had an error in excess of 10%. The study suggested that for readings below 72 mg/dL, there was a slight bias for that sensor to over read.

It is accepted that CGM may also fail to calibrate if initiated during hypoglycaemia. Within our study, the very early manual sensor insertion in this high risk study population of T1D newborns may have contributed to the withdrawal of five infants for whom no CGM data was available. The rate of sensor failure in this study was higher than has been observed in other published cohorts (21,34,35,40), which is likely a result of the earlier insertion, higher risk cohort, and newer sensors (with more difficult manual insertion) than were used in other studies. In some infants with low blood glucose levels initiation of sensor recording was delayed until stable glycaemia was obtained. This has been noted by others (26,35) and may result in an underestimation of exposure to neonatal hypoglycaemia in early life. Finally, it is a small single center feasibility study at a tertiary level academic hospital with a specialized diabetes pregnancy and full neonatal services.

We found a high burden of neonatal hypoglycaemia, with 15 of the 16 infants having at least one glucose concentration below 47 mg/dL (2.6 mmol/L), and five having at least one glucose below 18 mg/dL (1.0 mmol/L). Our study adds to the body of evidence suggesting that CGM can detect hypoglycaemia that goes undetected with routine heel-prick glucose monitoring, and may be useful in maintaining euglycaemia in neonates. We do not yet have an absolute threshold for what constitutes risk from neonatal hypoglycemia. Length of exposure to hypoglycaemia is likely to be more important, and CGM is a useful tool to assess overall exposure in a way that single heel-prick tests cannot.

Our study also provides insight into the impact of interventions to optimise glucose levels which will help in determining the potential balance between under and over treatment. Larger cohorts using early CGM, but with longer term targeted neurocognitive assessments, are needed to understand the complexities and risk of impaired metabolic transition and our clinical interventions in these infants.

Acknowledgements

The authors would like to thank all the pregnant women with type 1 diabetes who participated, along with their partners and families. We also acknowledge the invaluable support from the diabetes antenatal and postnatal care teams.

Contributors: HRM and KB designed the study protocol. ZAS, LT screened, enrolled and consented trial maternal (ZAS, HRM) and neonatal (ZAS, LT, KB) participants. LT, KB and ZAS inserted CGM sensors. ZAS analysed and ZAS, HRM, KB interpretated data. ZAS, HRM and KB wrote the manuscript, which all authors critically reviewed. ZAS, KB and HRM had full access to all the data and take responsibility for the integrity of the data, and accuracy of the analyses.

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