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Continuous Glucose Monitoring in Pregnancy: Importance of Analysing Temporal Profiles to Understand Clinical Outcomes

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Running title: Temporal glucose profiles in T1 pregnancy

Abstract

Objective: To determine if temporal glucose profiles differed between: 1) women who were randomized to continuous glucose monitoring (RT-CGM) or self-monitored blood glucose (SMBG); 2) women who used insulin pumps or multiple daily injections (MDI); 3) women whose infants were born large for gestational age (LGA) or not, by assessing CGM data obtained from the CONCEPTT trial.

Research Design and Methods: Standard summary metrics and functional data analysis (FDA) were applied to CGM data from the CONCEPTT trial (n=100 CGM; n=100 SMBG) taken at baseline, 24 and 34 weeks gestation. Multivariable regression analysis determined if temporal differences in 24 hour glucose profiles occurred between comparators in each of the three groups.

Results – FDA revealed that women using RT-CGM had significantly lower glucose [0.4-0.8 mmol/l (7-14mg/dL)] for 7 hrs/day (08.00-12.00 and 16.00-19.00) compared to SMBG. Women using pumps had significantly higher glucose [0.4-0.9 mmol/l (7-16mg/dL)] for 12 hrs/day (03.00 - 06.00, 13.00-18.00 and 20.30-00.30) at 24 weeks with no difference at 34 weeks compared to MDI. Women who had an LGA infant ran a significantly higher glucose by 0.4-0.7 mmol/l (7-13 mg/dL) for 4.5 hrs/day at baseline; by 0.4-0.9 mmol/l (7-16 mg/dL) for 16 hrs/day at 24 weeks; and by 0.4-0.7mmol/l (7-13 mg/dL) for 14 hrs/day at 34 weeks.

Conclusions: FDA of temporal glucose profiles gives important information about differences in glucose control and its timing, undetectable by standard summary metrics. Women using RT-CGM were able to achieve better daytime glucose control reducing fetal exposure to maternal glucose.

Keywords: Diabetes, pregnancy, macrosomia, glucose, Continuous Glucose Monitoring, functional data analysis, circadian, diurnal, birthweight, temporal.

Introduction

Maternal glucose is the major determinant of fetal growth, predicting large for gestational age (LGA) infants and neonatal outcomes (1). However, maternal glucose is dynamic, with glucose tolerance and insulin sensitivity varying across the 24h day with a circadian rhythmicity (2,3). Superimposed upon this there are the peaks and troughs in glucose, determined by the balance between insulin resistance and lifestyle/behavioural factors including diet, physical activity, energy expenditure, stress, sleep and shift work. Insulin sensitivity also varies across pregnancy, with insulin resistance increasing with gestation (4). It is this dynamic glucose signal to which the fetus is exposed in pregnancy. Continuous glucose monitoring (CGM) provides the most objective method of assessing this dynamic glucose signal in daily life (5). With up to 288 interstitial fluid glucose measurements per day, CGM accurately reflects blood glucose variations (5). Although standard summary metrics are recommended for the reporting of CGM (5,6) they do not give dynamic information about the timing of glucose excursions, thereby losing much of the detailed temporal glycemic information generated. We've pioneered the application of functional data analysis (FDA) to CGM data to extract shape information and identify glucose dysregulation that is undetectable by summary statistical measures (7,8). We have found that FDA is sensitive at detecting shorter periods of relative hyperglycemia that may not be detectable by summary metrics and enables accurate definition of time periods across the 24 hour day where differences in temporal glucose control occurs between groups and in relation to

clinical outcomes (7,8). Detecting this is particularly important in the context of pregnancy where even small increases in maternal glucose are related to poorer clinical outcomes (1).

The recent CONCEPTT trial showed that use of real-time continuous glucose monitoring (RT-CGM) during pregnancy in women with type 1 diabetes was associated with improved neonatal outcomes, including a lower incidence of large for gestational age (LGA), neonatal hypoglycemia and neonatal intensive care unit admission (9) compared to women who used only self-monitored blood glucose (SMBG). Whilst these improvements are likely to be attributable to improved glucose control, standard CGM metrics showed no differences in mean glucose, and showed only that pregnant RT-CGM users spent more time in the pregnancy glucose target range (3.5-7.8 mmol/l or 63-140mg/dL) and less time hyperglycemic (9). The effect of using pumps or multiple daily insulin injections (MDI) was also explored and unexpectedly showed that women using pumps had poorer pregnancy outcomes, with significantly more neonatal hypoglycaemia and neonatal intensive care admissions, (10). Standard CGM metrics showed only that pump users spent 5% more time above the glucose target range at 24 weeks gestation and 5% less time in range at 24 weeks than women on MDI (10). The lack of comprehensive differences in standard CGM metrics, whilst showing differences in neonatal outcomes suggests that there may be differences in temporal glucose profiles that were not detected by the standard CGM metrics.

The objective of the present study was therefore to perform FDA on the CGM data obtained in the CONCEPTT trial to determine if temporal differences in 24 hour glucose profiles occurred between: 1) women who were randomized to RT-CGM or SMBG; 2) women who used insulin pumps or MDI; 3) women whose infants had LGA or not.

Research design and methods

Study design

Full details of the CONCEPTT clinical trial protocol have previously been published (9, 11). Women with type 1 diabetes were eligible if they were aged 18–40 years, had 12 months' duration of diabetes, and were on an intensive insulin regimen using either a pump or MDI. Pregnant women had to have a live singleton fetus confirmed by ultrasound before 14 weeks' gestational age and an HbA1c level between 6.5 and 10% (48–86 mmol/mol). After a run-in period where eligible women wore a masked CGM (iPro2 Professional CGM, Medtronic, Northridge, CA, USA) for at least 96 h, women were randomized to the intervention, where they received a RT-CGM (Guardian REAL-Time or MiniMed Minilink system, both Medtronic, Northridge, CA) that required calibration by SMBG, or to the control group, where they were instructed to continue with their usual SMBG testing at least seven times per day (pre meals and 1hr post meals, plus before bed). The women were reviewed as per standard clinical care 1-2 weekly and algorithms were used to help patients and their teams decide on treatment adjustments in both arms. Randomization was stratified by insulin delivery system (pump or MDI) and by baseline HbA1c level (<7.5 vs. $\geq 7.5\%$ or 58 mmol/mol during pregnancy). Women in the SMBG pregnant group were asked to wear a masked CGM on two further occasions at 24 and 34 weeks. RT-CGM data was obtained at 24 and 34 weeks gestation from the RT-CGM group for comparison. LGA was defined as birthweight ≥ 90 th percentile using Gestation Related Optimal Weight (GROW) software (12) which adjusts for infant sex and gestational age, maternal height, weight, parity, and ethnicity. This current analysis includes data from women who were in the pregnant arm of the original study who had complete birthweight data (n=200) and where we had >96 hours of continuous data.

Study oversight

The study was approved by the Health Research Authority, East of England Research Ethics Committee (12/EE/0310) for all UK sites, and at each individual centre for all other sites.

Participants provided written informed consent.

Standard CGM metrics

The standard range of summary metrics was calculated for each CGM measurement period (baseline, 24 and 34 weeks gestation) including: mean CGM glucose levels; the percentage of time spent within the pregnancy glucose target range (3.5-7.8 mmol/L [63-140 mg/dL]); time spent above (>7.8mmol/l [>140 mg/dL]) and below (<3.5 mmol/l [<63 mg/dL]) target range. Measures of glycemic variability: standard deviation (SD) and coefficient of variation (CV) of mean CGM glucose levels were calculated. Comparisons of means between groups were made using a student's t-test.

Functional Data Analysis

For each individual the mean of the four or more days of temporal CGM data obtained at each glucose time point across the 24 hour day was taken. In this way, there was no missing data for performing the FDA. Each of the glucose values recorded during the measurement episodes (at baseline, 24 and 34 weeks gestation) was assumed to be dependent upon (rather than independent of) the preceding glucose levels. Changes in glucose over time were therefore assumed to be progressive, occurring in a trend or sequence that could be considered 'smooth' (in a mathematical sense) without step changes from one measurement to the next. For this reason, sequential glucose measurements from each measurement episode were modeled as trajectories by calculating continuous mathematical functions of CGM-derived glucose measurements collected every five minutes throughout that measurement episode. These trajectories were modeled using the technique of fitting B-

splines to the repeated measures (7,8,13). This technique generates a polynomial function that describes the curve (or ‘spline’) used to model changes in glucose levels over time for each participant, with splines required to pass through measured glucose values at discrete time points (called ‘knots’) during each 24 hour period. At each of these knots the spline function was required to be continuous (i.e. with no breaks or step changes) so that the function remained mathematically smooth. Knots were placed at 30 minute intervals over each 24-hour measurement period, with data from measurements recorded during the 4 hours either side of midnight (i.e., from 20h00-04h00) repeated at the beginning and end to eliminate artefactual edge effects. In this way the splines provided a smooth mathematical function describing glucose levels recorded across each measurement episode – hence its name ‘functional data analysis’.

Multivariable regression analysis was used for the FDA generated glucose function to establish the relationship between maternal glucose levels in 1) women who were randomized to RT-CGM compared to those on SMBG (combining the 24 and 34 weeks data); 2) women who used insulin pumps compared to MDI (at baseline, 24 and 34 weeks gestation); 3) women whose infants had LGA compared to those that didn’t (at baseline, 24 and 34 weeks gestation). No adjustment was made for multiple comparisons: these specific questions were defined prior to performing FDA; and confidence intervals were used to assess the significance of the relationship. All statistical analyses were conducted in Stata (14) and R (15)

Results

CGM and neonatal outcome data was available from 200 women in the pregnant arm of the CONCEPTT trial (100 RT-CGM and 100 SMBG). The participant characteristics are shown in Table 1.

1) RT-CGM versus SMBG

Standard CGM Metrics

The results of the CGM metrics are shown in Table 2A. There were no differences in mean glucose between groups at any time point across pregnancy. However, when mean glucose was calculated separately for day and night there was a significantly higher glucose overnight at 24 weeks, with a significantly lower glucose during the day at 24 weeks. There were no differences in any other standard measures at 24 weeks. At 34 weeks, women randomized to RT-CGM had significantly more time in pregnancy glucose target range and less time spent above target compared to SMBG controls. Women using RT-CGM had significantly less glucose variability at 34 weeks, with lower SD and CV glucose.

Functional Data Analysis

Figure 1 illustrates the difference in CGM glucose across the 24 hour day in women who were randomized to RT-CGM compared to SMBG after applying FDA. Women who used RT-CGM ran a significantly lower glucose by 0.4-0.8 mmol/l (7-14mg/dL) for 7 hours during the daytime (08.00-12.00 and 16.00-19.00). There were no significant differences in glucose overnight.

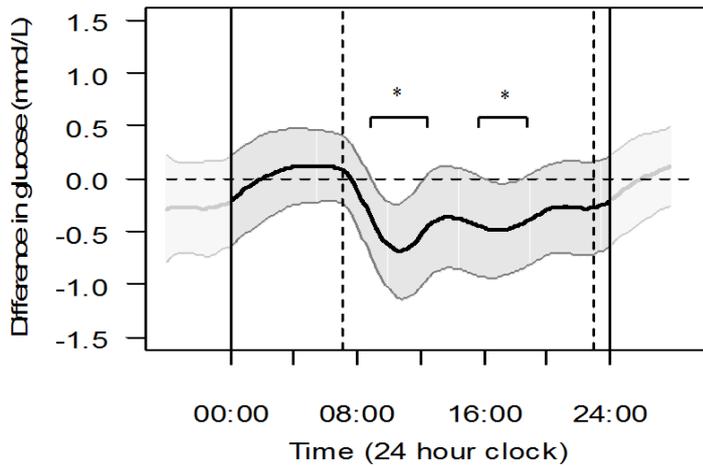


Figure 1. Difference in mean temporal glucose levels across the 24 hour day, assessed by FDA (at 24 and 34 weeks gestation combined), between those women who were randomized to RT-CGM (represented by the dark wavy line) compared to those using SMBG (represented by the horizontal zero dotted line) with 95% pointwise CIs (gray section). Where both of the CIs sit to the same side of 0.0 it indicates a significant difference. Significant differences using 95% CIs are shown by *. Dashed vertical lines represent ‘daytime’ 0700 h and 2300 h.

2) Pumps versus MDI

Standard CGM Metrics

Standard CGM metrics, shown in Table 2B, showed a significantly higher mean glucose, with higher mean glucose shown both overnight and during the day at 24 weeks gestation in those women on pumps, and more time spent above target. There were no differences in glucose variability measures at any point.

Functional Data Analysis

Figure 2A shows that women who used insulin pumps had significantly lower glucose levels by 0.4-0.9 mmol/l (7-16mg/dL) for 5.5 hours of the 24 hour day (07.30-11.30 and 20.00-

21.30) at baseline; but significantly higher glucose levels by 0.4-0.9 mmol/l (7-16mg/dL) for a total of 12 hours a day (03.00 - 06.00, 13.00-18.00 and 20.30-00.30) at 24 weeks gestation and no difference in glucose levels at 34 weeks gestation. These differences were predominantly seen during daytime hours.

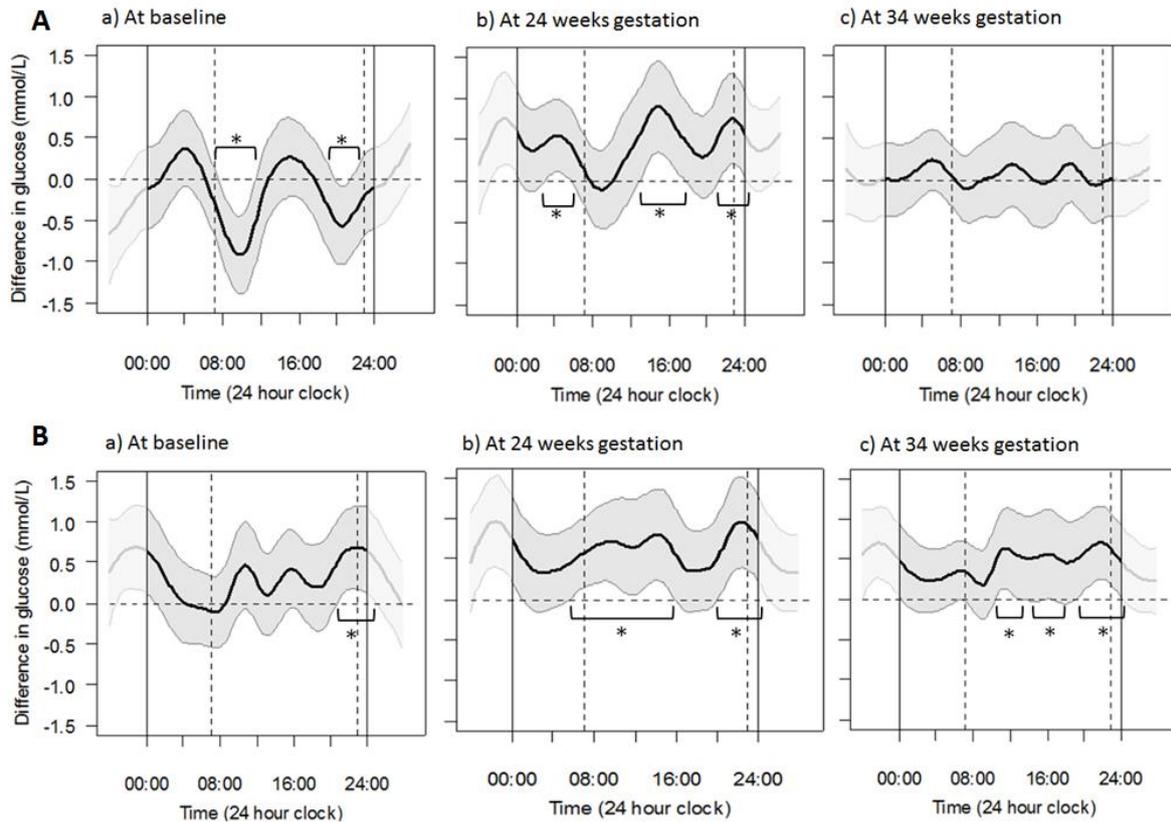


Figure 2. Difference in mean temporal glucose levels across the 24 hour day, assessed by FDA in: A) women who used pumps (represented by dark wavy line) compared to those on MDI (represented by the horizontal zero dotted line) with 95% pointwise CIs (gray section); B) women who gave birth to an LGA infant (represented by the dark wavy line) compared to those who didn't (represented by the horizontal zero dotted line) with 95% pointwise CIs (gray section). Significant differences using 95% CIs are shown by *. Dashed vertical lines represent 'daytime' 0700 h and 2300 h.

3) LGA versus non-LGA

Standard CGM Metrics

Women who went on to have an LGA infant had significantly higher mean glucose at 24 and 34 weeks gestation, shown in Table 2C. Both day and night-time mean glucose were significantly higher in the LGA group at 24 weeks, but at 34 weeks only the night-time glucose was significantly higher. Time spent in pregnancy target range was significantly lower in each trimester in those women who had an LGA infant, with significantly more time spent above the pregnancy target range of 3.5-7.8 mmol/l (63-140mg/dL) throughout pregnancy. There was significantly greater glucose variability in the first and second trimesters in those women who went on to have an LGA infant as demonstrated by SD and CV glucose.

Functional Data Analysis

Figure 2B shows that women who had an LGA infant ran a significantly higher glucose by 0.4-0.7 mmol/l (7-13 mg/dL) for 4.5 hours from 21.00 at baseline; a significantly higher glucose by 0.4-0.9 mmol/l (7-16 mg/dL) for 16 hours a day at 24 weeks gestation; and significantly higher glucose by 0.4-0.7mmol/l (7-13 mg/dL) for 14 hours a day at 34 weeks gestation. These higher glucose levels were predominantly seen during daytime hours.

Conclusions

By applying FDA to the CGM data obtained in CONCEPTT, we are able to clearly identify differences in maternal glucose and determine when and for how long across the 24 hour day this is occurring, even when standard CGM metrics fail to detect a difference. In doing so, this study demonstrates that pregnant women randomized to RT-CGM have lower glucose

during the daytime than women using SMBG alone. It shows that although women using insulin pumps start pregnancy with better glucose control, they have a higher glucose for 12 hours during the daytime during mid pregnancy, only achieving comparable glucose control to women using MDI, in late pregnancy. Finally, it shows that women who delivered an LGA infant, ran a higher glucose throughout pregnancy, sustained for up to 16 hours per day at 24 weeks gestation.

The CONCEPTT trial showed a beneficial effect of using RT-CGM on neonatal outcomes and its data has supported the adoption of 'time in range' targets for using CGM in type 1 diabetes pregnancy (6,9). Whilst improving 'time in range' by 5% improves pregnancy outcomes, it is not clear which periods of the day are best targeted to achieve this (9). Our current analysis helps to define this. Although there was no difference in mean glucose between RT-CGM and SMBG using standard CGM metrics, it did not mean that there were no significant differences in glucose at certain time points across the day. FDA allows this visualization showing that using RT-CGM leads to reduced fetal exposure to daytime maternal glucose. This suggests that RT-CGM data helps women to observe the impact of carbohydrate ingestion on the daytime glucose profiles better than SMBG does, and allows them to take appropriate action to prevent/manage this. It is worth noting that the women using RT-CGM only had significantly better glucose control for 7 hrs/day and that although LGA was reduced in the RT-CGM group, LGA rates remained high (9). Given that we showed that women who go on to have LGA infants run higher glucose for 16hrs/day, it suggests that there is room for further improvement in daytime glucose control in the RT-CGM group.

It was interesting that contrary to expectations women using pumps had poorer neonatal outcomes than women using MDI (10) yet the original analysis was unable to show any significant differences in glucose between the two groups using standard CGM metrics, except that pump users spent significantly less time below 3.5 mmol/l (63 mg/dL) compared to MDI, throughout pregnancy and 5% less time in range at 24 weeks (10). The differences in temporal glucose profiles seen between women using pumps or MDI using FDA provide new insights into why these outcomes occurred. The FDA clearly shows that women using insulin pumps entered pregnancy with better first trimester glucose control. This advantage is however lost as pregnancy progresses, with evidence of substantially worse daytime glucose control at 24 weeks gestation. It again suggests that mealtime glucose control is particularly important, and that clinicians and patients are possibly less effective at optimizing mid-trimester insulin to carbohydrate during pregnancy using insulin pumps. No differences were seen in total insulin doses between pumps and MDI, but data was not available on the insulin:carbohydrate or the basal:bolus ratios used (10,16).

The standard CGM metrics readily showed significant differences when it came to LGA, with a higher mean glucose at 24 and 34 weeks gestation; significantly lower time spent in pregnancy target range in each trimester, significantly higher time spent above the pregnancy target range of 3.5-7.8 mmol/l (63-140mg/dL) throughout pregnancy; and greater glucose variability in the first and second trimesters in those women who went on to have an LGA infant. This is consistent with the recent findings of an observational study of 186 pregnant women with type 1 diabetes using CGM in Sweden which showed that higher mean CGM glucose levels in the second and third trimester were significantly associated with LGA, as well as less time spent in pregnancy target range, and greater SD in second trimester (19). The FDA performed in our study again provides further insights, showing that there are

actually periods of relatively higher glucose as early as the first trimester that are associated with LGA and that it is predominantly higher daytime glucose control that is contributing to the higher overall mean glucose observed with standard CGM metrics. This supports our earlier work on FDA in a much smaller cohort of women with type 1 and type 2 diabetes where we showed that a significantly higher glucose across the daytime in mid and late gestation is associated with LGA in women being treated to tight, postprandial glucose targets (7). It seems likely that the greater the duration of time exposed to even small amounts of extra glucose is important in the context of fetal growth in pregnancy.

It is interesting that we have previously observed a different glucose profile associated with LGA in women being treated for gestational diabetes (8). In that study we saw that daytime glucose control was achieved, but that nocturnal glucose control was suboptimal, with women who went on to have LGA infants running significantly higher glucose for 6 hours overnight (8). This difference may reflect the different emphasis in management between the two types of diabetes: the focus of management in gestational diabetes is very much on making significant dietary changes, whereas we do not consider that this is always the case in type 1 diabetes where the focus is more on adjustment of insulin to accommodate 'normal eating' (18).

Overall this analysis of temporal glucose profiles shows that women who have poorer pregnancy outcomes (women on SMBG, pumps, and those with LGA infants) run relatively higher glucoses during the daytime than women who don't. The reason for this is likely to be related to carbohydrate ingestion, indicating that greater attention is needed to improving the management of mealtime and snack hyperglycemia in women with type 1 diabetes during pregnancy. The higher daytime glucose is particularly pronounced at 24 weeks gestation, and

we hypothesize that this also reflects changes in insulin responsiveness at this stage in pregnancy (16). Whilst there are no changes in glucose bioavailability or postprandial glucose appearance between early and late gestation in type 1 diabetes there are significant delays in postprandial glucose disposal as pregnancy advances, possibly due to a combination of increased peripheral insulin resistance and a slower achievement of maximum insulin concentration leading to a more prolonged hyperglycemia (17). We know from dietary assessment of women in CONCEPTT that their food choices, especially of between meal snacks tended to be of highly processed carbohydrates of low nutritional value (18) and that this leads to a rapid increase in glucose with a lag time for any extra insulin to catch up and bring it down. Going forward the solutions are to bolus insulin 15 minutes before the meal, increasing to 40 minutes later in pregnancy (17), replace rapidly absorbed carbohydrate rich meals for more slowly absorbed ones, or advise postprandial physical activity to enhance peripheral glucose uptake. It would seem sensible to emphasize making more healthy dietary changes in women with type 1 diabetes whilst pregnant to help reduce daytime hyperglycemia, given that currently ‘normal’ eating habits are far from ideal (18).

The strengths of this study are that it used data from a large, multi-center, international, randomized controlled trial. It is thus representative of the women being managed for type 1 diabetes in routine clinical care internationally. CGM provides far more frequent glucose measurements than SMBG, and far more information on short-to-medium term trends in glucose levels than either SMBG or HbA1c. CGM nonetheless has recognized imitations, particularly with regard to the quality of glucose readings during rapid blood glucose changes and in situations of hypoglycemia. The measurement of interstitial glucose may also not reflect precisely the levels of blood glucose. CGM data was only obtained at three time points across gestation in this study, which may not be representative of glucose control at other times in pregnancy, and we acknowledge that recently published consensus guidelines

suggest that 2 weeks of CGM data are preferred for analysis (although this recommendation is based on data outside of pregnancy) (5). It is worth noting that although significant differences were observed, these are still small sample sizes, and larger numbers would be beneficial in future work. Other limitations of this study were that we didn't have detailed dietary information on timing of meal/snack/drink ingestion, which means that although it is likely, we cannot definitively say that the raised daytime glucose was due to this.

In summary, FDA of CGM glucose profiles gives important information about differences in glucose control, largely undetectable by standard CGM metrics, including detail on the timing and duration of these differences. Whilst FDA is best suited to explore population level differences in glucose profiles, the equivalent on an individual basis clinically would be the ambulatory glucose profile. Regular review of this throughout pregnancy would enable a focus on meal choices, together with a more aggressive approach to bringing forward insulin bolus timing and increasing insulin doses especially mid pregnancy, aiming for small, but sustained, improvements in daytime glucose levels.

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Contributors: GRL and EMS are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy

of the data analysis. GRL and EMS wrote the manuscript, which all authors critically reviewed.

Conflicts of Interest: EMS has received honoraria for speaking from Abbott Diabetes Care and Eli-Lilly; HRM serves on the Medtronic European Scientific Advisory Board. GRL and DF have no potential conflicts of interest relevant to this article.

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Table 1: Participant characteristics

	Total	Intervention RT-CGM	SMBG	Treatment Pumps	MDI	Birthweight LGA	Non-LGA
Number	200	100	100	90	110	122	78
BMI kg/m ² (SD)	25.7 (4.6)	26.2 (5.1)	25.2 (3.9)	26.0 (4.8)	25.4 (4.4)	25.5 (4.4)	26.0 (4.8)
Primiparous n (%)	98 (49)	49 (49)	49 (49)	42 (47)	56 (51)	61 (50)	37 (47)
Mean gestation at birth in weeks (SD)	36.9 (1.7)	37.2 (1.4)	36.8 (1.9)	36.8 (1.8)	37.1 (1.6)	36.9 (1.6)	37.1 (1.9)
Birthweight in kg (SD)	3.56 (0.71)	3.55 (0.65)	3.58 (0.78)	3.53 (0.75)	3.59 (0.69)	3.91 (0.58)	3.03 (0.56)
GROW birthweight centile (SD)	82.0 (25.8)	78.4 (26.8)	85.5 (24.4)	79.4 (28.4)	84.1 (23.4)	97.8 (28.2)	57.2 (26.2)

Data are expressed as means (SD) or n (%). SD = Standard deviation

Table 2: Standard summary metrics of CGM data across pregnancy comparing: A) RT-CGM group to SMBG controls; B) pump to MDI; C) LGA to non-LGA

	Baseline		24 weeks		34 weeks	
A)	CGM	SMBG	CGM	SMBG	CGM	SMBG
Number	100	100	89	90	77	76
Mean glucose mmol/l (SD)	7.3 (1.2)	7.6 (1.1)	7.6 (1.2)	7.8 (1.3)	6.7 (0.9)	7.0 (1.1)
00:01-06:00 Mean glucose mmol/l (SD)	6.7 (1.5)	7.1 (1.4)	7.2 (1.4)	7.0 (1.4)	6.2 (1.0)	6.3 (1.2)
06:01-00:00 Mean glucose mmol/l (SD)	7.5 (1.3)	7.8 (1.2)	7.7 (1.3)	8.1 (1.4)	7.0 (1.0)	7.3 (1.2)
% time 3.5-7.8 mmol/l (SD)	51.7 (13.0)	51.5 (13.7)	53.0 (15.5)	49.8 (15.0)	67.6 (12.6)	61.3 (15.5)
% time below 3.5 mmol/l (SD)	10.0 (7.7)	7.8 (6.4)	4.8 (4.8)	5.5 (5.7)	4.6 (4.9)	5.7 (5.2)
% time above 7.8 mmol/l (SD)	38.4 (14.9)	40.6 (13.8)	42.3 (17.6)	44.7 (16.0)	27.9 (13.4)	33.1 (15.0)
Mean individual SD (SD)	3.1 (0.8)	3.2 (0.8)	2.7 (0.6)	2.9 (0.7)	2.2 (0.5)	2.5 (0.7)
Mean individual CV % (SD)	42.2 (8.7)	42.4 (8.1)	35.6 (5.9)	36.9 (7.2)	32.5 (5.8)	34.9 (7.6)
B)	Pump	MDI	Pump	MDI	Pump	MDI

Number	90	110	81	98	71	82
Mean glucose mmol/l (SD)	7.4 (1.2)	7.5 (1.1)	7.9 (1.3)	7.5 (1.1)	6.9 (0.9)	6.8 (1.1)
00:01-06:00 Mean glucose mmol/l (SD)	7.6 (1.3)	7.8 (1.2)	7.4 (1.4)	6.9 (1.4)	6.3 (1.1)	6.2 (1.1)
06:01-00:00 Mean glucose mmol/l (SD)	6.9 (1.6)	6.9 (1.4)	8.1 (1.4)	7.7 (1.3)	7.1 (1.0)	7.1 (1.2)
% time 3.5-7.8 mmol/l (SD)	53.6 (13.4)	50.0 (13.1)	48.8 (16.5)	53.6 (13.9)	64.1 (13.3)	64.8 (15.4)
% time below 3.5 mmol/l (SD)	8.1 (6.3)	9.5 (7.8)	4.5 (4.5)	5.7 (5.7)	5.0 (5.2)	5.2 (4.9)
% time above 7.8 mmol/l (SD)	38.3 (15.2)	40.4 (13.6)	46.7 (17.8)	40.8 (15.5)	31.0 (14.2)	30.0 (14.7)
Mean individual SD (SD)	3.1 (0.8)	3.2 (0.8)	2.8 (0.7)	2.8 (0.7)	2.3 (0.6)	2.3 (0.7)
Mean individual CV % (SD)	41.3 (7.3)	43.1 (9.1)	35.6 (6.7)	36.7 (6.5)	33.7 (6.8)	33.7 (6.8)
C)	LGA	Non-LGA	LGA	Non-LGA	LGA	Non-LGA
Number	122	78	111	68	96	57
Mean glucose mmol/l (SD)	7.6 (1.2)	7.3 (1.2)	7.9 (1.2)	7.3 (1.2)	7.0 (1.1)	6.6 (0.8)
00:01-06:00 Mean glucose mmol/l (SD)	7.0 (1.4)	6.8 (1.6)	7.3 (1.4)	6.9 (1.4)	7.3 (1.2)	6.8 (0.9)
06:01-00:00 Mean glucose mmol/l (SD)	7.8 (1.3)	7.5 (1.2)	8.1 (1.3)	7.5 (1.3)	6.4 (1.1)	6.1 (1.0)
% time 3.5-7.8 mmol/l (SD)	49.6 (13.8)	54.7 (13.6)	48.2 (14.9)	56.6 (14.4)	62.6 (11.8)	67.6 (11.8)
% time below 3.5 mmol/l (SD)	9.2 (7.0)	8.4 (7.5)	5.0 (15.3)	5.4 (5.1)	4.5 (4.6)	6.2 (5.6)
% time above 7.8 mmol/l (SD)	41.2 (14.4)	36.8 (14.0)	46.9 (16.3)	38.0 (16.2)	33.0 (15.3)	26.2 (11.7)
Mean individual SD (SD)	3.3 (0.8)	3.0 (0.9)	2.9 (0.6)	2.6 (0.7)	2.4 (0.7)	2.2 (0.5)
Mean individual CV % (SD)	43.3 (8.5)	41.1 (8.1)	36.6 (6.8)	35.5 (6.3)	33.6 (7.2)	33.8 (6.2)

Bold for p<0.05 in a t-test comparing the difference.

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