
Article:
Scott, EM orcid.org/0000-0001-5395-8261, Murphy, HR, Kristensen, KH et al. (5 more authors) (Accepted: 2022) Continuous glucose monitoring metrics and birthweight: informing management of type 1 diabetes throughout pregnancy. Diabetes Care. ISSN 0149-5992 (In Press)

American Diabetes Association. Diabetes Care

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Journal:	*Diabetes Care*
Manuscript ID	DC22-0078.R2
Manuscript Type:	Original Article: Clinical Care/Education/Nutrition/Psychosocial Research
Date Submitted by the Author:	n/a
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Continuous glucose monitoring metrics and birthweight: informing management of type 1 diabetes throughout pregnancy.

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Word Count: Structured Abstract: 251; Text 30952; Figures: 3; Tables: 1; Animations of figures: 2; References 30

Running title: CGM metrics and birthweight

Structured Abstract

Objective: To determine gestational weekly changes in continuous glucose monitoring **(**CGM) metrics and 24hr glucose profiles, and their relationship to infant birthweight in pregnant women with type 1 diabetes.

Research Design and Methods: An analysis of >10.5 million CGM glucose measures from 386 pregnant women with type 1 diabetes, from two international, multicentre studies. CGM glucose metrics and 24hr glucose profiles were calculated for each gestational week and the relationship to normal (10-90th percentile) and large (>90th percentile) for gestational age (LGA) birthweight infants determined.

Results: Mean CGM glucose concentration fell and percentage of time spent in the pregnancy target range 3.5-7.8 mmol/L (63-140mg/dL) increased in the first 10 weeks of pregnancy, plateaued until 28 weeks gestation, before further improvements in mean glucose and percentage time-in-range until delivery. The maternal CGM glucose metrics diverged at 10 weeks gestation, with significantly lower mean CGM glucose concentration (7.1mmol/L 95% CI 7.05-7.15 [127.8mg/dL 95% CI 126.9-128.7] vs.7.5mmol/L 95% CI 7.45-7.55 [135mg/dL 95% CI 134.1-135.9]) and higher percentage time-in-range (55% [95% CI 54-56] vs.50% [95% CI 49-51]) in women who had normal versus LGA. The 24hr glucose profiles were significantly higher across the day from 10 weeks gestation in LGA.

Conclusion: Normal birthweight is associated with achieving a significantly lower mean CGM glucose concentration across the 24-hour day and higher CGM time-in-range from before the end of the first trimester, emphasizing the need for a shift in clinical management, with increased focus on using weekly CGM glucose targets for optimising maternal glycemia from early pregnancy.

Despite advances in antenatal diabetes care, 60% of liveborn infants of mothers with type 1 diabetes (T1D) are born with a birthweight that is large for gestational age (LGA), which is unchanged from the first reports of 'giant' babies in 1941[1-5]. LGA birthweight greater than the 90th percentile is associated with increased rates of obstetric and neonatal complications (preterm and operative delivery, neonatal hypoglycaemia and neonatal intensive care admission)[2,6]. In severe cases, additional manoeuvres are required to release the shoulders (shoulder dystocia) that can result in nerve injury, fractures and hypoxic brain injury. This is the third most litigated obstetric-related complication in the UK, incurring escalating National Health Service (NHS) costs[7]. Furthermore, LGA birthweight predisposes the infant to developing obesity, type 2 diabetes and cardiovascular disease persisting into adulthood[8,9]. Optimal glucose control to prevent these outcomes, is the major focus of antenatal care[10,11].

Continuous glucose monitoring (CGM) is revolutionizing diabetes care[12,13]. Compared to HbA1c or self-monitored capillary glucose, CGM provides up to 288 glucose measures/day, depending on the device used, providing detailed information about glucose changes across the 24-hour day[12,13].It demonstrates complete 24hr glucose profiles with percentage of time spent in the target glucose ranges (time-in-range), and high and low glucose excursions which inform therapy decisions, thereby informing diabetes self-management[12,13]. In T1D pregnancies CGM improves maternal glucose, reducing LGA and associated neonatal complications[4]. However, despite this technology becoming standard care[10,11] LGA prevalence remains high [2,4,5].

Pregnancy is a dynamic state of continuous metabolic adaptation with changes in insulin sensitivity and glucose tolerance throughout[14]. Pregnant women with T1D are reviewed frequently and therapeutic decisions are made based on the previous week's mean CGM glucose data (a combination of glucose summary metrics and 24hr glucose profiles), yet the

weekly CGM glucose metrics and 24hr profiles associated with a normal birthweight baby are unknown. Thus, despite widespread CGM use, international diabetes guidelines do not include gestationally appropriate CGM glucose targets[10-13]. This analysis was designed to inform clinical care by determining gestational changes in CGM glucose metrics and 24hr profiles weekly during pregnancy and the relationship of these to birthweight outcomes.

Research Design and Methods

Study design

The CGM data from two existing studies were combined[4,5]. Full details of the CONCEPTT international clinical trial were previously published[4]. Pregnant women aged 18–40 years, with HbA1c between 6.5 and 10% (48–86 mmol/mol) using a pump or multiple daily insulin injections (MDI) and a singleton fetus were randomized to continuous real-time CGM (Guardian REAL-time or MiniMed Minilink system, Medtronic, Northridge, CA) or control group, where they performed self-monitored blood glucose (SMBG) measurements at least seven times per day. CGM data was downloaded monthly in the RT-CGM group, and at baseline, 24- and 34-weeks' gestation in the control group.

Full details of the Swedish observational study have also been published[5]. It included women aged 18 years or more, with a singleton pregnancy, using a Freestyle Libre or Dexcom G4 CGM device compatible with the internet-based Diasend system (Glooko, Gothenburg, Sweden) at two tertiary clinics in Sweden (Skåne University Hospital and Östra/Sahlgrenska University Hospital).

Women in both studies received specialist antenatal care, with clinic visits every 2 to 4 weeks. This analysis combines all the available raw downloaded continuous glucose data from 200

women in CONCEPTT and 186 women from the Swedish study, with complete birthweight records. Each participant only had one, singleton pregnancy. 26% (102/386) of participants were using CGM prior to pregnancy. The number of participants contributing at least four days CGM data for each gestational week is detailed in supplemental data (Table S1).

Study oversight

The CONCEPTT 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 center for all other sites. The Swedish study was approved by the Ethics Committee of Lund University (2017/322) and was conducted in accordance with the Swedish Act on Ethics Review of Research Involving Humans and the Swedish Act on Personal Data. All women gave written informed consent.

Obstetric data and outcomes

Electronic antenatal and perinatal records provided data on maternal age, parity, BMI, insulin regimen, birthweight, gestational age at birth and sex of infant. LGA was defined as birthweight ≥90th percentile using Gestation Related Optimal Weight (GROW) software which adjusts for infant sex and gestational age, maternal height, weight, parity and ethnicity[15].

Standard CGM metrics

For each participant, and for each gestational week, the mean of each 5-minute time interval was taken from the four or more days of temporal CGM data obtained at each time point across the 24-hour day. A standard range of summary CGM metrics were calculated for each week's gestation from the raw downloaded glucose data[12]. These included: mean CGM glucose concentration; the percentage of time spent within the pregnancy target glucose range 3.5-7.8

mmol/L (63-140 mg/dL) (TIR); time spent above 7.8mmol/L (>140 mg/dL) (TAR) and below 3.5 mmol/L (<63 mg/dL) target range (TBR). Measures of glycemic variability included coefficient of variation of mean CGM glucose (CV) and mean amplitude of glucose excursions (MAGE)[12]. Weekly summary metrics were plotted for women with and without LGA birthweight infants. These were fitted using Epanechnikov Kernel-weighted local polynomial smoothing, with 95% confidence intervals to assess the significance of the relationship.

Visualisation of 24 hr Glucose Profiles

We performed functional data analysis as previously described, to establish the population level 24-hour glucose profiles each week across gestation[16-20]. For each participant, and for each gestational week, the mean of each 5-minute time interval was taken from the four or more days of temporal CGM data obtained at each time point across the 24-hour day. In this way, there were no missing data for applying the FDA. 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. Sequential glucose concentrations from each measurement episode were modeled as trajectories by calculating continuous mathematical functions of CGM-derived glucose values[20].

The CGM-glucose trajectories were modeled using the technique of fitting B-splines to the repeated measures[20]. This 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 though 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 20.00-04.00) repeated at the beginning and end to eliminate artefactual edge effects.

Multivariable regression analysis was used for the FDA generated glucose function to establish the relationship between weekly maternal glucose levels in women with and without LGA birthweight infants. 95% Confidence intervals were used to assess the significance of the relationship. All statistical analyses were conducted in Stata[21] and R[22].

Results

Overview of study population

Baseline characteristics of the 386 participants are shown in Table 1. Swedish participants delivered slightly later, with higher birthweight, fewer preterm births and caesarean deliveries but remarkably similar customised birthweight percentiles (83%) and LGA rates (60%).

Evolution of standard CGM metrics

CGM metrics, weekly across gestation with 95% confidence intervals, are shown in Figure 1. Mean glucose fell steeply in the first 10 weeks gestation in both normal and LGA birthweight mothers. By 10 weeks gestation, a significant divergence in mean glucose emerged between women who go on to have a normal sized versus LGA birthweight infant (7.1 mmol/L vs 7.6 mmol/L [128mg/dL vs 137mg/dL]). This between group divergence persisted during 10-20 weeks, increased further during 20-30 weeks gestation, after which glucose fell by approximately 1mmol/L (18mg/dL) in both groups, reaching a nadir after 36 weeks gestation.

CGM percentage time-in-range started at 40% (9.6 hours/day) in early pregnancy, with significant between group differences from ~6-8 weeks gestation. Women who go on to have

a normal sized versus LGA birthweight infant reached 57% versus 50% time-in-range by ~10 weeks gestation. Similar to mean glucose, the divergence between groups CGM time-in-range persisted during 10-20 weeks, increased further during 20-30 weeks, and remained significantly lower (by 8-10%) in the LGA birthweight group until 34 weeks gestation. There were no between group differences after 36 weeks with both groups only achieving the recommended international consensus target of ≥70% time-in-range (16 hours 48 mins), late in the third trimester.

As expected from the changes in mean CGM glucose and percentage time-in-range, both groups achieved striking early pregnancy reductions in hyperglycaemia. CGM percentage time-above-range (>7.8mmol/L [140mg/dL]) decreased from 60% to 40% by 10 weeks gestation. From 10 weeks onwards, a significant 5% time-above-range difference persisted between women with a normal sized versus LGA birthweight infant (40 vs 35%). This between group divergence also increased, with increasing hyperglycaemia in the LGA birthweight group during 18-28 weeks gestation. CGM percentage time-above-range then falls by ~15% in both groups, with mothers of normal sized infants only reaching the recommended international consensus target of ≤25% (6 hours/day), late in the third trimester.

Maternal hypoglycaemia, as measured by CGM percentage time-below-range varied more than other glucose metrics, peaking around 10% (2.4 hours/day) at 10 weeks. There were no between group differences until ~14 weeks gestation, at which point time-below-range progressively decreased in the LGA birthweight group reaching 6% by 30 weeks. CGM percentage time-below-range remained above the recommended international consensus target of ≤4% (1 hour/day), never falling below 8% in women with normal sized babies. CGM percentage time-below-range increased by 1.5% in both groups after 30 weeks gestation.

Like hypoglycaemia, glucose variability peaked in early pregnancy (CV 38-40% at ~10 weeks gestation). This was followed by a sustained reduction in glucose variability measures throughout pregnancy with less glycaemic variability in mothers of LGA birthweight infants between 24-30 weeks gestation. Mean amplitude glucose excursions (MAGE) also started high with sustained gestational improvements and remained slightly higher in mothers of LGA birthweight infants throughout 10-36 weeks gestation.

Evolution of 24 hr glucose profiles

Functional data analysis (Figure 2 and Animation 1) shows week-by-week changes in the mean CGM glucose profile across the 24-hour day. Women entered pregnancy (weeks 0-4) with CGM glucose levels that were predominantly above the upper target range limit of 7.8 mmol/L(140mg/dL). Mean CGM glucose fell progressively until 10 weeks, plateaued between 10-30 weeks gestation, until a further fall from ~30 weeks. The initial CGM glucose trajectory demonstrates a high overnight glucose pattern followed by a morning (08.00-12.00) dip. Thereafter, diurnal glucose levels increased with each meal as the day progresses, leading to high nocturnal glucose levels. From seven weeks gestation onwards, women consistently demonstrated a nocturnal glucose dip, with higher daytime glucose levels and clear daytime peaks (approximately 10.00 and 22.00) which persisted until the end of pregnancy.

Evolution of 24 hr glucose profiles across gestation in relation to LGA

Multivariable regression of the functional data analysis (Figure 3 and Animation 2) demonstrates the relationship of mean CGM glucose profiles across the 24-hour day in women who went on to have LGA, compared to a normal birthweight. At 11 weeks there was a significantly higher daytime glucose pattern in mothers of LGA infants, and from 12 weeks

onwards, this higher CGM glucose profile is evident for most of the 24-hour day, with 'daytime' peaks persisting until 35 weeks gestation.

Conclusions

Internationally, manywomen with T1D are using CGM to optimise their glucose levels during pregnancy. Our analysis shows in detail how CGM glucose metrics change across pregnancy and the CGM glucose levels that are associated with having a normal birthweight baby. In doing so it provides pregnant women and their clinical teams, with the weekly CGM targets to aim for across pregnancy. Despite widespread CGM use, glycaemic control targets are currently based on HbA1c, which has well documented gestational limitations[10,11,23]. These data will inform international clinical guidelines and support patients and clinicians to use CGM more effectively, which will hopefully help to improve glycemia and reduce LGA.

In clinical practice, the most recent week's CGM metrics are reviewed, whilst the 24 hr profiles are used to spot patterns of glucose excursions across the 24hr day when optimising glucose management can achieve more time-in-range. We have analysed our data to reproduce this clinical situation at a population level, providing weekly CGM metrics and 24hr profiles. This extensive temporal information demonstrates the central role of maternal glucose to the pathogenesis of LGA from early gestation. Importantly, we show a sustained 0.5 mmol/L (9 mg/dL) difference in mean CGM glucose concentration across the 24-hour day, every week from 10 weeks gestation onwards in women who have an LGA infant. This small but clinically relevant[24] difference persists for the rest of pregnancy, with increasing glycaemic divergence until 30 weeks gestation. By 12 weeks gestation, the fetal pancreas can respond to maternal glucose by increasing endogenous insulin production[25]. This leads to the incremental accrual

of adipose tissue, fetal growth acceleration and LGA birthweight in over two thirds of T1D pregancies[25].

Our data shows that achieving tight CGM glucose targets, from early pregnancy (10-12 weeks gestation) are associated with normal birthweight outcomes. Irrespective of baseline maternal glycaemia, first trimester mean glucose levels decrease rapidly without initial differences between women who go onto have a normal sized or LGA birthweight infant. However, from 10 weeks gestation achieving a mean glucose of ≤7 mmol/l (≤126 mg/dL) was associated with having a normal sized infant. Irrespective of the baseline maternal glucose level, early intervention to optimise glycemia (specifically mean CGM glucose, CGM time-in-range and CGM time-above-range) within the first 10 gestational weeks may help to reduce fetal growth acceleration and complications associated with LGA birthweight that are traditionally associated with glycaemia in late pregnancy.

The recommended glucose target range for pregnancy is 3.5 – 7.8 mmol/L (63-140 mg/dL)[10-13]. By examining the weekly 24 hr profiles we show that, before 10 weeks gestation most maternal glucose levels remain above target across the 24-hour day. Thereafter, the 24-hour CGM glucose profiles show that maternal glucose levels exceed the recommended target particularly at 10.00 and 22.00, which is consistent with post-prandial rises following breakfast and evening meals. This is more pronounced in those women who have LGA infants. For optimal antenatal glycaemia and to achieve more time in range, targeting maternal dietary intake, and the timing and accuracy of carbohydrate counting and prandial insulin doses for the morning and evening mealtimes is required[26]. This may require more emphasis on education and support pre-pregnancy and in early pregnancy. Future research should examine whether tighter overnight glucose targets (e.g 3.5-5.5mmol/l) are applicable or safely achievable.

Free from the increasingly recognised gestational limitations of HbA1c, which fails to detect the mid-trimester plateauing or deteriorating glycemia[23], CGM time-in-range has become a key metric for monitoring antenatal glucose levels[27]. An international consensus guideline has proposed that a CGM time-in-range target of >70% is recommended in pregnancy[13]. This target is currently challenging to achieve, with the majority of women using CGM in addition to intensive insulin therapy (insulin pumps or multiple daily injections) only reaching this after 34 weeks gestation[4,5]. Our current analysis suggests that aiming for a CGM time-in-range of ≥ 55-60 % by 10 weeks gestation may be sufficient for normal fetal growth, aiming to achieve 70% thereafter. Additional dietary attention, psycho-educational support, and technological interventions, such as closed-loop insulin delivery, maybe required for women who do not achieve their pregnancy CGM glucose targets by 10 weeks[19].

Our study demonstrates that, in addition to CGM time-in-range, mean glucose and time-above-range are also clinically relevant CGM metrics in relation to birthweight. Achieving a mean glucose of ≤7.0 mmol/L (≤126mg/dL) and spending no more than 35% time-above-range by 10 weeks, was associated with normal fetal growth.

The first trimester fall in mean glucose concentration, which plateaus until 28 weeks gestation, followed by a smaller third trimester reduction is remarkably consistent in women whose babies do and do not develop LGA. This supports previous work and suggests a large physiological component to the glycaemic changes which mirror gestational changes in maternal insulin sensitivity, increasing in early gestation, decreasing during the second trimester, before increasing in the late third trimester[14,28]. There is considerable clinician anxiety around a fall in maternal insulin requirements in the last trimester suggesting placental

insufficiency[29]. Our data indicates that a fall in mean glucose, accompanied by a fall in CGM time-above-range and rise in time-in-range is not unexpected in late pregnancy.

This is the largest cohort of CGM data from pregnant women with T1D. It included women using pumps and multiple daily injections, reflecting contemporary antenatal diabetes management. Combining two datasets makes it widely representative of women with T1D internationally and provides statistical power to assess glycemic differences across gestation. A potential limitation is that one dataset was obtained from a randomised controlled trial whereas the other was from an observational study. In doing so we obtained data from several different CGM devices, of varying accuracy. However, whilst time in range may vary slightly between some devices, the mean glucose has been shown to be consistent[30]. Despite having 386 participants, data in any given week were available from fewer women, such that we had less CGM data at the very start and end of pregnancy, as women presented for antenatal care and delivered their babies at different gestational ages (mean 37 weeks) which is likely to have contributed to the wider 95% confidence interval at these times. We did not have data available for all participants on the gestational week of their first antenatal clinic visit or when in relation to this the CGM was started. Whilst we used all eligible CGM raw data, we do not have the level of detail available on each participant to know if they chose not to wear the sensor, or if the sensor malfunctioned or came off early, that may have contributed to loss of data. We acknowledge that sensor compliance was likely to be lower than seen with the newer generation CGM systems.

In summary, our results give unprecedented insight into glucose physiology across gestation and the relationship between CGM glucose levels and birthweight in pregnant women with T1D. We have shown that normal birthweight is associated with achieving a significantly lower

mean CGM glucose concentration (sustained across the 24-hour day), higher CGM time-in-range and lower CGM time-above-range from before the end of the first trimester, emphasizing the need for a paradigm shift in clinical management, with increased focus on using weekly CGM glucose targets for optimising maternal glycemia from early pregnancy.

Table 1: Participant characteristics

	Study				Birthweight		
	Total	CONCEPTT	Sweden	statistic (p)	LGA	Non-LGA	statistic (p)
Number of participants	386	200	186		232	154	
Mean age in years (SD)	37.21	36.97 (1.69)	37.49 (2.03)	-2.73 (1.00)	37.14 (1.63)	37.34 (2.19)	0.99 (0.84)
Number of European descent (%)	346 (90)	178 (89)	173 (93)	-1.37 (0.17)	206 (89)	145 (94)	1.80 (0.07)
Mean diabetes duration in years (SD)	15.95	16.49 (7.66)	15.39 (8.12)	1.36 (0.91)	16.13 (7.89)	15.69 (7.89)	-0.54 (0.70)
Number insulin delivery by pump (%)	144 (37)	90 (45)	54 (29)	3.24 (<0.01)	94 (41)	50 (32)	-1.60 (0.11)
Mean first Trimester HbA1c mmol/mol (SD)	56.6 (9.9)	57.1 (7.8)	55.7 (12.4)	1.30 (0.19)	56.9 (9.9)	56.1 (9.9)	-0.71 (0.48)
Mean first Trimester HbA1c % (SD)	7.3 (1.6)	7.4 (1.4)	7.2 (1.9)	1.30 (0.19)	7.4 (1.6)	7.3 (1.6)	-0.71 (0.48)
Mean BMI kg/m^2 (SD)	25.8 (4.6)	25.7 (4.6)	25.9 (4.7)	-0.34 (0.73)	25.9 (4.7)	25.4 (4.4)	-0.33 (0.74)
Number primiparous (%)	187 (48)	98 (49)	89 (48)	0.22 (0.82)	66 (28)	121 (78)	0.08 (0.93
Mean gestation birth weeks (SD)	37.2 (1.9)	36.9 (1.7)	37.5 (2.0)	-3.18 (<0.01)	37.0 (1.6)	37.3 (2.2)	-1.55 (0.12)
Number preterm delivery <37 weeks (%)	132 (34)	80 (40)	52 (28)	2.49 (0.01)	83 (36)	49 (32)	-0.80 (0.42)
Number caesarean section (%)	224 (58)	137 (69)	87 (47)	4.32 (<0.01)	150 (65)	74 (48)	-3.24 (<0.01)
Mean birthweight in kg (SD)	3.69	3.56 (0.71)	3.82 (0.72)	3.47 (<0.01)	4.00 (0.55)	3.00 (0.57)	-12.94 (<0.01)
Mean birthweight percentile[#] (SD)	82.7	82.0 (25.8)	83.6 (23.4)	-0.64 (0.52)	98.1 (2.67)	59.6 (25.0)	-23.22 (<0.01)
Number LGA ≥ 90th percentile (%)	232 (60)	122 (61)	110 (59)	-1.17 (0.24)	225 (97)	7 (26)	-14.73 (<0.01)

Results are given as n (%) or mean (SD)). T-test used where mean (SD) are given (t), percentage uses a 2-sample test of proportion (z).

Birthweight was adjusted for infant sex and gestational age, maternal height, weight, parity and ethnicity, for singleton pregnancies using the Gestation Related Optimal Weight (GROW) centile tool[1]

Figure 1. Evolution of CGM metrics (vertical axis) across gestation (horizontal axis) in women with type 1 diabetes. Women who delivered an LGA infant (>90th centile) (red line) are compared with those who did not (blue line). Each is fitted with a local polynomial smoothed curve and the 95% confidence interval is the shaded grey band. A) Mean CGM glucose; B) percentage of time spent in pregnancy target range TIR 3.5-7.8mmol/L; C) percentage of time spent above pregnancy target range TAR >7.8 mmol/l; D) percentage of time spent below target range TBR <3.5 mmol/L; E) Coefficient of Variation; F) Mean Amplitude of Glucose Excursions (MAGE)

Figure 2. Functional line fit showing the evolution of 24-hour mean CGM glucose profiles across gestation in women with type 1 diabetes. Mean glucose (mmol/L) and 95% confidence interval by gestational age in weeks. The dotted horizontal line represents 7.8 mmol/L (upper limit of recommended target range for pregnancy).

Figure 3. Functional data analysis showing the differences in mean temporal glucose levels across the 24-hr day and its evolution across gestation in women with type 1 diabetes who delivered an LGA (>90th centile) infant (represented by the dark wavy line) compared with those who did not (represented by the horizontal zero dotted line) with 95% pointwise Confidence Interval (gray section). The time period where the 95% Confidence Interval sit on the same side of 0.0, indicates a significant difference in glucose - for clarity these time periods have been illustrated as an example on Gestational week 11 by *, but this is not shown on the subsequent graphs.

Animation 1. Functional line fit showing the evolution of 24-hr mean CGM glucose profiles across gestation in women with type 1 diabetes. Mean glucose (mmol/L) and 95%

confidence interval by gestational age in weeks. The dotted horizontal line represents 7.8 mmol/L upper limit of recommended pregnancy target range.

Animation 2. Functional data analysis showing the differences in mean temporal glucose levels across the 24-hr day and its evolution across gestation in women with type 1 diabetes who gave birth to an LGA (>90th centile on GROW) infant (represented by the dark wavy line) compared with those who did not (represented by the horizontal zero dotted line) with 95% pointwise Confidence Interval (grey section). The time period where the 95% Confidence Interval sit on the same side of 0.0, indicates a significant difference in glucose.

Acknowledgements: The authors would like to thank all the women with type 1 diabetes who participated. We also acknowledge the invaluable support from the 31 clinical care teams and the CONCEPTT Steering Committee: Denice S Feig, Helen R Murphy, Elisabeth Asztalos, Jon F R Barrett, Rosa Corcoy, Alberto de Leiva, Lois E Donovan, J Moshe Hod, Lois Jovanovic, Erin Keely, Craig Kollman, Ruth McManus, Kellie E Murphy, Katrina Ruedy and George Tomlinson; and the antenatal diabetes clinical team at Skåne University Hospital and Östra/Sahlgrenska University Hospital in Sweden, in particular Anastasia Katsarou, Nael Shaat, Annika Dotevall, Verena Sengpiel, Anders Elfvin and Ulrika Sandgren; and the CGM data management team at the Parker Institute, Copenhagen, Denmark.

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 this data analysis. EMS and HRM designed this study. GRL performed the statistical data analysis. HRM, DF were responsible for CONCEPTT study design and data collection; KK,

KK, LEO, KB were responsible for the Swedish study design and data collection. Preliminary results were discussed with DF, KK and KB. EMS, HRM and GRL 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. DSF has received funds from Novo Nordisk for serving on an Expert Panel. GRL, DF, KK, KK, LEO and KB have no potential conflicts of interest relevant to this article.

Funding: The CONCEPTT trial was funded by Juvenile Diabetes Research Foundation (JDRF) grants #17-2011-533, and grants under the JDRF Canadian Clinical Trial Network, a public-private partnership including JDRF and FedDev Ontario and supported by JDRF #80-2010-585. Medtronic supplied the CGM sensors and CGM systems at reduced cost. GRL, EMS and HRM were part funded by HEFCE and MRC (MR/T001828/1). ES and HM were part funded by NIHR (EME 16/35/01), and HM was part funded by NIHR (CDF-2013-06-035). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the UK Department of Health. The Swedish study was funded by a research grant from Region Skåne, Sweden, and The Oak Foundation.

Data availability Data are available on request from the authors.

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Continuous glucose monitoring metrics and birthweight: informing management of type 1 diabetes throughout pregnancy.

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Word Count: Structured Abstract: 251; Text 3095; Figures: 3; Tables: 1; Animations of figures: 2; References 30

Running title: CGM metrics and birthweight

Structured Abstract

Objective: To determine gestational weekly changes in continuous glucose monitoring **(**CGM) metrics and 24hr glucose profiles, and their relationship to infant birthweight in pregnant women with type 1 diabetes.

Research Design and Methods: An analysis of >10.5 million CGM glucose measures from 386 pregnant women with type 1 diabetes, from two international, multicentre studies. CGM glucose metrics and 24hr glucose profiles were calculated for each gestational week and the relationship to normal (10-90th percentile) and large (>90th percentile) for gestational age (LGA) birthweight infants determined.

Results: Mean CGM glucose concentration fell and percentage of time spent in the pregnancy target range 3.5-7.8 mmol/L (63-140mg/dL) increased in the first 10 weeks of pregnancy, plateaued until 28 weeks gestation, before further improvements in mean glucose and percentage time-in-range until delivery. The maternal CGM glucose metrics diverged at 10 weeks gestation, with significantly lower mean CGM glucose concentration (7.1mmol/L 95% CI 7.05-7.15 [127.8mg/dL 95% CI 126.9-128.7] vs.7.5mmol/L 95% CI 7.45-7.55 [135mg/dL 95% CI 134.1-135.9]) and higher percentage time-in-range (55% [95% CI 54-56] vs.50% [95% CI 49-51]) in women who had normal versus LGA. The 24hr glucose profiles were significantly higher across the day from 10 weeks gestation in LGA.

Conclusion: Normal birthweight is associated with achieving a significantly lower mean CGM glucose concentration across the 24-hour day and higher CGM time-in-range from before the end of the first trimester, emphasizing the need for a shift in clinical management, with increased focus on using weekly CGM glucose targets for optimising maternal glycemia from early pregnancy.

Despite advances in antenatal diabetes care, 60% of liveborn infants of mothers with type 1 diabetes (T1D) are born with a birthweight that is large for gestational age (LGA), which is unchanged from the first reports of 'giant' babies in 1941[1-5]. LGA birthweight greater than the 90th percentile is associated with increased rates of obstetric and neonatal complications (preterm and operative delivery, neonatal hypoglycaemia and neonatal intensive care admission)[2,6]. In severe cases, additional manoeuvres are required to release the shoulders (shoulder dystocia) that can result in nerve injury, fractures and hypoxic brain injury. This is the third most litigated obstetric-related complication in the UK, incurring escalating National Health Service (NHS) costs[7]. Furthermore, LGA birthweight predisposes the infant to developing obesity, type 2 diabetes and cardiovascular disease persisting into adulthood[8,9]. Optimal glucose control to prevent these outcomes, is the major focus of antenatal care[10,11].

Continuous glucose monitoring (CGM) is revolutionizing diabetes care[12,13]. Compared to HbA1c or self-monitored capillary glucose, CGM provides up to 288 glucose measures/day, depending on the device used, providing detailed information about glucose changes across the 24-hour day[12,13].It demonstrates complete 24hr glucose profiles with percentage of time spent in the target glucose ranges (time-in-range), and high and low glucose excursions which inform therapy decisions, thereby informing diabetes self-management[12,13]. In T1D pregnancies CGM improves maternal glucose, reducing LGA and associated neonatal complications[4]. However, despite this technology becoming standard care[10,11] LGA prevalence remains high [2,4,5].

Pregnancy is a dynamic state of continuous metabolic adaptation with changes in insulin sensitivity and glucose tolerance throughout[14]. Pregnant women with T1D are reviewed frequently and therapeutic decisions are made based on the previous week's mean CGM glucose data (a combination of glucose summary metrics and 24hr glucose profiles), yet the

weekly CGM glucose metrics and 24hr profiles associated with a normal birthweight baby are unknown. Thus, despite widespread CGM use, international diabetes guidelines do not include gestationally appropriate CGM glucose targets[10-13]. This analysis was designed to inform clinical care by determining gestational changes in CGM glucose metrics and 24hr profiles weekly during pregnancy and the relationship of these to birthweight outcomes.

Research Design and Methods

Study design

The CGM data from two existing studies were combined[4,5]. Full details of the CONCEPTT international clinical trial were previously published[4]. Pregnant women aged 18–40 years, with HbA1c between 6.5 and 10% (48–86 mmol/mol) using a pump or multiple daily insulin injections (MDI) and a singleton fetus were randomized to continuous real-time CGM (Guardian REAL-time or MiniMed Minilink system, Medtronic, Northridge, CA) or control group, where they performed self-monitored blood glucose (SMBG) measurements at least seven times per day. CGM data was downloaded monthly in the RT-CGM group, and at baseline, 24- and 34-weeks' gestation in the control group.

Full details of the Swedish observational study have also been published[5]. It included women aged 18 years or more, with a singleton pregnancy, using a Freestyle Libre or Dexcom G4 CGM device compatible with the internet-based Diasend system (Glooko, Gothenburg, Sweden) at two tertiary clinics in Sweden (Skåne University Hospital and Östra/Sahlgrenska University Hospital).

Women in both studies received specialist antenatal care, with clinic visits every 2 to 4 weeks. This analysis combines all the available raw downloaded continuous glucose data from 200

women in CONCEPTT and 186 women from the Swedish study, with complete birthweight records. Each participant only had one, singleton pregnancy. 26% (102/386) of participants were using CGM prior to pregnancy. The number of participants contributing at least four days CGM data for each gestational week is detailed in supplemental data (Table S1).

Study oversight

The CONCEPTT 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 center for all other sites. The Swedish study was approved by the Ethics Committee of Lund University (2017/322) and was conducted in accordance with the Swedish Act on Ethics Review of Research Involving Humans and the Swedish Act on Personal Data. All women gave written informed consent.

Obstetric data and outcomes

Electronic antenatal and perinatal records provided data on maternal age, parity, BMI, insulin regimen, birthweight, gestational age at birth and sex of infant. LGA was defined as birthweight ≥90th percentile using Gestation Related Optimal Weight (GROW) software which adjusts for infant sex and gestational age, maternal height, weight, parity and ethnicity[15].

Standard CGM metrics

For each participant, and for each gestational week, the mean of each 5-minute time interval was taken from the four or more days of temporal CGM data obtained at each time point across the 24-hour day. A standard range of summary CGM metrics were calculated for each week's gestation from the raw downloaded glucose data[12]. These included: mean CGM glucose concentration; the percentage of time spent within the pregnancy target glucose range 3.5-7.8

mmol/L (63-140 mg/dL) (TIR); time spent above 7.8mmol/L (>140 mg/dL) (TAR) and below 3.5 mmol/L (<63 mg/dL) target range (TBR). Measures of glycemic variability included coefficient of variation of mean CGM glucose (CV) and mean amplitude of glucose excursions (MAGE)[12]. Weekly summary metrics were plotted for women with and without LGA birthweight infants. These were fitted using Epanechnikov Kernel-weighted local polynomial smoothing, with 95% confidence intervals to assess the significance of the relationship.

Visualisation of 24 hr Glucose Profiles

We performed functional data analysis as previously described, to establish the population level 24-hour glucose profiles each week across gestation[16-20]. For each participant, and for each gestational week, the mean of each 5-minute time interval was taken from the four or more days of temporal CGM data obtained at each time point across the 24-hour day. In this way, there were no missing data for applying the FDA. 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. Sequential glucose concentrations from each measurement episode were modeled as trajectories by calculating continuous mathematical functions of CGM-derived glucose values[20].

The CGM-glucose trajectories were modeled using the technique of fitting B-splines to the repeated measures[20]. This 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 though 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 20.00-04.00) repeated at the beginning and end to eliminate artefactual edge effects.

Multivariable regression analysis was used for the FDA generated glucose function to establish the relationship between weekly maternal glucose levels in women with and without LGA birthweight infants. 95% Confidence intervals were used to assess the significance of the relationship. All statistical analyses were conducted in Stata[21] and R[22].

Results

Overview of study population

Baseline characteristics of the 386 participants are shown in Table 1. Swedish participants delivered slightly later, with higher birthweight, fewer preterm births and caesarean deliveries but remarkably similar customised birthweight percentiles (83%) and LGA rates (60%).

Evolution of standard CGM metrics

CGM metrics, weekly across gestation with 95% confidence intervals, are shown in Figure 1. Mean glucose fell steeply in the first 10 weeks gestation in both normal and LGA birthweight mothers. By 10 weeks gestation, a significant divergence in mean glucose emerged between women who go on to have a normal sized versus LGA birthweight infant (7.1 mmol/L vs 7.6 mmol/L [128mg/dL vs 137mg/dL]). This between group divergence persisted during 10-20 weeks, increased further during 20-30 weeks gestation, after which glucose fell by approximately 1mmol/L (18mg/dL) in both groups, reaching a nadir after 36 weeks gestation.

CGM percentage time-in-range started at 40% (9.6 hours/day) in early pregnancy, with significant between group differences from ~6-8 weeks gestation. Women who go on to have

a normal sized versus LGA birthweight infant reached 57% versus 50% time-in-range by ~10 weeks gestation. Similar to mean glucose, the divergence between groups CGM time-in-range persisted during 10-20 weeks, increased further during 20-30 weeks, and remained significantly lower (by 8-10%) in the LGA birthweight group until 34 weeks gestation. There were no between group differences after 36 weeks with both groups only achieving the recommended international consensus target of ≥70% time-in-range (16 hours 48 mins), late in the third trimester.

As expected from the changes in mean CGM glucose and percentage time-in-range, both groups achieved striking early pregnancy reductions in hyperglycaemia. CGM percentage time-above-range (>7.8mmol/L [140mg/dL]) decreased from 60% to 40% by 10 weeks gestation. From 10 weeks onwards, a significant 5% time-above-range difference persisted between women with a normal sized versus LGA birthweight infant (40 vs 35%). This between group divergence also increased, with increasing hyperglycaemia in the LGA birthweight group during 18-28 weeks gestation. CGM percentage time-above-range then falls by ~15% in both groups, with mothers of normal sized infants only reaching the recommended international consensus target of ≤25% (6 hours/day), late in the third trimester.

Maternal hypoglycaemia, as measured by CGM percentage time-below-range varied more than other glucose metrics, peaking around 10% (2.4 hours/day) at 10 weeks. There were no between group differences until ~14 weeks gestation, at which point time-below-range progressively decreased in the LGA birthweight group reaching 6% by 30 weeks. CGM percentage time-below-range remained above the recommended international consensus target of ≤4% (1 hour/day), never falling below 8% in women with normal sized babies. CGM percentage time-below-range increased by 1.5% in both groups after 30 weeks gestation.

Like hypoglycaemia, glucose variability peaked in early pregnancy (CV 38-40% at ~10 weeks gestation). This was followed by a sustained reduction in glucose variability measures throughout pregnancy with less glycaemic variability in mothers of LGA birthweight infants between 24-30 weeks gestation. Mean amplitude glucose excursions (MAGE) also started high with sustained gestational improvements and remained slightly higher in mothers of LGA birthweight infants throughout 10-36 weeks gestation.

Evolution of 24 hr glucose profiles

Functional data analysis (Figure 2 and Animation 1) shows week-by-week changes in the mean CGM glucose profile across the 24-hour day. Women entered pregnancy (weeks 0-4) with CGM glucose levels that were predominantly above the upper target range limit of 7.8 mmol/L(140mg/dL). Mean CGM glucose fell progressively until 10 weeks, plateaued between 10-30 weeks gestation, until a further fall from ~30 weeks. The initial CGM glucose trajectory demonstrates a high overnight glucose pattern followed by a morning (08.00-12.00) dip. Thereafter, diurnal glucose levels increased with each meal as the day progresses, leading to high nocturnal glucose levels. From seven weeks gestation onwards, women consistently demonstrated a nocturnal glucose dip, with higher daytime glucose levels and clear daytime peaks (approximately 10.00 and 22.00) which persisted until the end of pregnancy.

Evolution of 24 hr glucose profiles across gestation in relation to LGA

Multivariable regression of the functional data analysis (Figure 3 and Animation 2) demonstrates the relationship of mean CGM glucose profiles across the 24-hour day in women who went on to have LGA, compared to a normal birthweight. At 11 weeks there was a significantly higher daytime glucose pattern in mothers of LGA infants, and from 12 weeks

onwards, this higher CGM glucose profile is evident for most of the 24-hour day, with 'daytime' peaks persisting until 35 weeks gestation.

Conclusions

Internationally, manywomen with T1D are using CGM to optimise their glucose levels during pregnancy. Our analysis shows in detail how CGM glucose metrics change across pregnancy and the CGM glucose levels that are associated with having a normal birthweight baby. In doing so it provides pregnant women and their clinical teams, with the weekly CGM targets to aim for across pregnancy. Despite widespread CGM use, glycaemic control targets are currently based on HbA1c, which has well documented gestational limitations[10,11,23]. These data will inform international clinical guidelines and support patients and clinicians to use CGM more effectively, which will hopefully help to improve glycemia and reduce LGA.

In clinical practice, the most recent week's CGM metrics are reviewed, whilst the 24 hr profiles are used to spot patterns of glucose excursions across the 24hr day when optimising glucose management can achieve more time-in-range. We have analysed our data to reproduce this clinical situation at a population level, providing weekly CGM metrics and 24hr profiles. This extensive temporal information demonstrates the central role of maternal glucose to the pathogenesis of LGA from early gestation. Importantly, we show a sustained 0.5 mmol/L (9 mg/dL) difference in mean CGM glucose concentration across the 24-hour day, every week from 10 weeks gestation onwards in women who have an LGA infant. This small but clinically relevant[24] difference persists for the rest of pregnancy, with increasing glycaemic divergence until 30 weeks gestation. By 12 weeks gestation, the fetal pancreas can respond to maternal glucose by increasing endogenous insulin production[25]. This leads to the incremental accrual

of adipose tissue, fetal growth acceleration and LGA birthweight in over two thirds of T1D pregancies[25].

Our data show that achieving tight CGM glucose targets, from early pregnancy (10-12 weeks gestation) are associated with normal birthweight outcomes. Irrespective of baseline maternal glycaemia, first trimester mean glucose levels decrease rapidly without initial differences between women who go onto have a normal sized or LGA birthweight infant. However, from 10 weeks gestation achieving a mean glucose of ≤7 mmol/l (≤126 mg/dL) was associated with having a normal sized infant. Irrespective of the baseline maternal glucose level, early intervention to optimise glycemia (specifically mean CGM glucose, CGM time-in-range and CGM time-above-range) within the first 10 gestational weeks may help to reduce fetal growth acceleration and complications associated with LGA birthweight that are traditionally associated with glycaemia in late pregnancy.

The recommended glucose target range for pregnancy is 3.5 – 7.8 mmol/L (63-140 mg/dL)[10-13]. By examining the weekly 24 hr profiles we show that, before 10 weeks gestation most maternal glucose levels remain above target across the 24-hour day. Thereafter, the 24-hour CGM glucose profiles show that maternal glucose levels exceed the recommended target particularly at 10.00 and 22.00, which is consistent with post-prandial rises following breakfast and evening meals. This is more pronounced in those women who have LGA infants. For optimal antenatal glycaemia and to achieve more time in range, targeting maternal dietary intake, and the timing and accuracy of carbohydrate counting and prandial insulin doses for the morning and evening mealtimes is required[26]. This may require more emphasis on education and support pre-pregnancy and in early pregnancy. Future research should examine whether tighter overnight glucose targets (e.g 3.5-5.5mmol/l) are applicable or safely achievable.

Free from the increasingly recognised gestational limitations of HbA1c, which fails to detect the mid-trimester plateauing or deteriorating glycemia[23], CGM time-in-range has become a key metric for monitoring antenatal glucose levels[27]. An international consensus guideline has proposed that a CGM time-in-range target of >70% is recommended in pregnancy[13]. This target is currently challenging to achieve, with the majority of women using CGM in addition to intensive insulin therapy (insulin pumps or multiple daily injections) only reaching this after 34 weeks gestation[4,5]. Our current analysis suggests that aiming for a CGM time-in-range of ≥ 55-60 % by 10 weeks gestation may be sufficient for normal fetal growth, aiming to achieve 70% thereafter. Additional dietary attention, psycho-educational support, and technological interventions, such as closed-loop insulin delivery, maybe required for women who do not achieve their pregnancy CGM glucose targets by 10 weeks[19].

Our study demonstrates that, in addition to CGM time-in-range, mean glucose and time-above-range are also clinically relevant CGM metrics in relation to birthweight. Achieving a mean glucose of ≤7.0 mmol/L (≤126mg/dL) and spending no more than 35% time-above-range by 10 weeks, was associated with normal fetal growth.

The first trimester fall in mean glucose concentration, which plateaus until 28 weeks gestation, followed by a smaller third trimester reduction is remarkably consistent in women whose babies do and do not develop LGA. This supports previous work and suggests a large physiological component to the glycaemic changes which mirror gestational changes in maternal insulin sensitivity, increasing in early gestation, decreasing during the second trimester, before increasing in the late third trimester[14,28]. There is considerable clinician anxiety around a fall in maternal insulin requirements in the last trimester suggesting placental

insufficiency[29]. Our data indicates that a fall in mean glucose, accompanied by a fall in CGM time-above-range and rise in time-in-range is not unexpected in late pregnancy.

This is the largest cohort of CGM data from pregnant women with T1D. It included women using pumps and multiple daily injections, reflecting contemporary antenatal diabetes management. Combining two datasets makes it widely representative of women with T1D internationally and provides statistical power to assess glycemic differences across gestation. A potential limitation is that one dataset was obtained from a randomised controlled trial whereas the other was from an observational study. In doing so we obtained data from several different CGM devices, of varying accuracy. However, whilst time in range may vary slightly between some devices, the mean glucose has been shown to be consistent[30]. Despite having 386 participants, data in any given week were available from fewer women, such that we had less CGM data at the very start and end of pregnancy, as women presented for antenatal care and delivered their babies at different gestational ages (mean 37 weeks) which is likely to have contributed to the wider 95% confidence interval at these times. We did not have data available for all participants on the gestational week of their first antenatal clinic visit or when in relation to this the CGM was started. Whilst we used all eligible CGM raw data, we do not have the level of detail available on each participant to know if they chose not to wear the sensor, or if the sensor malfunctioned or came off early, that may have contributed to loss of data. We acknowledge that sensor compliance was likely to be lower than seen with the newer generation CGM systems.

In summary, our results give unprecedented insight into glucose physiology across gestation and the relationship between CGM glucose levels and birthweight in pregnant women with T1D. We have shown that normal birthweight is associated with achieving a significantly lower

mean CGM glucose concentration (sustained across the 24-hour day), higher CGM time-in-range and lower CGM time-above-range from before the end of the first trimester, emphasizing the need for a paradigm shift in clinical management, with increased focus on using weekly CGM glucose targets for optimising maternal glycemia from early pregnancy.

Table 1: Participant characteristics

	Study				Birthweight		
	Total	CONCEPTT	Sweden	statistic (p)	LGA	Non-LGA	statistic (p)
Number of participants	386	200	186		232	154	
Mean age in years (SD)	37.21	36.97 (1.69)	37.49 (2.03)	-2.73 (1.00)	37.14 (1.63)	37.34 (2.19)	0.99 (0.84)
Number of European descent (%)	346 (90)	178 (89)	173 (93)	-1.37 (0.17)	206 (89)	145 (94)	1.80 (0.07)
Mean diabetes duration in years (SD)	15.95	16.49 (7.66)	15.39 (8.12)	1.36 (0.91)	16.13 (7.89)	15.69 (7.89)	-0.54 (0.70)
Number insulin delivery by pump (%)	144 (37)	90 (45)	54 (29)	3.24 (<0.01)	94 (41)	50 (32)	-1.60 (0.11)
Mean first Trimester HbA1c mmol/mol (SD)	56.6 (9.9)	57.1 (7.8)	55.7 (12.4)	1.30 (0.19)	56.9 (9.9)	56.1 (9.9)	-0.71 (0.48)
Mean first Trimester HbA1c % (SD)	7.3 (1.6)	7.4 (1.4)	7.2 (1.9)	1.30 (0.19)	7.4 (1.6)	7.3 (1.6)	-0.71 (0.48)
Mean BMI kg/m^2 (SD)	25.8 (4.6)	25.7 (4.6)	25.9 (4.7)	-0.34 (0.73)	25.9 (4.7)	25.4 (4.4)	-0.33 (0.74)
Number primiparous (%)	187 (48)	98 (49)	89 (48)	0.22 (0.82)	66 (28)	121 (78)	0.08 (0.93
Mean gestation birth weeks (SD)	37.2 (1.9)	36.9 (1.7)	37.5 (2.0)	-3.18 (<0.01)	37.0 (1.6)	37.3 (2.2)	-1.55 (0.12)
Number preterm delivery <37 weeks (%)	132 (34)	80 (40)	52 (28)	2.49 (0.01)	83 (36)	49 (32)	-0.80 (0.42)
Number caesarean section (%)	224 (58)	137 (69)	87 (47)	4.32 (<0.01)	150 (65)	74 (48)	-3.24 (<0.01)
Mean birthweight in kg (SD)	3.69	3.56 (0.71)	3.82 (0.72)	3.47 (<0.01)	4.00 (0.55)	3.00 (0.57)	-12.94 (<0.01)
Mean birthweight percentile[#] (SD)	82.7	82.0 (25.8)	83.6 (23.4)	-0.64 (0.52)	98.1 (2.67)	59.6 (25.0)	-23.22 (<0.01)
Number LGA ≥ 90th percentile (%)	232 (60)	122 (61)	110 (59)	-1.17 (0.24)	225 (97)	7 (26)	-14.73 (<0.01)

Results are given as n (%) or mean (SD)). T-test used where mean (SD) are given (t), percentage uses a 2-sample test of proportion (z).

Birthweight was adjusted for infant sex and gestational age, maternal height, weight, parity and ethnicity, for singleton pregnancies using the Gestation Related Optimal Weight (GROW) centile tool[1]

Figure 1. Evolution of CGM metrics (vertical axis) across gestation (horizontal axis) in women with type 1 diabetes. Women who delivered an LGA infant (>90th centile) (red line) are compared with those who did not (blue line). Each is fitted with a local polynomial smoothed curve and the 95% confidence interval is the shaded grey band. A) Mean CGM glucose; B) percentage of time spent in pregnancy target range TIR 3.5-7.8mmol/L; C) percentage of time spent above pregnancy target range TAR >7.8 mmol/l; D) percentage of time spent below target range TBR <3.5 mmol/L; E) Coefficient of Variation; F) Mean Amplitude of Glucose Excursions (MAGE)

Figure 2. Functional line fit showing the evolution of 24-hour mean CGM glucose profiles across gestation in women with type 1 diabetes. Mean glucose (mmol/L) and 95% confidence interval by gestational age in weeks. The dotted horizontal line represents 7.8 mmol/L (upper limit of recommended target range for pregnancy).

Figure 3. Functional data analysis showing the differences in mean temporal glucose levels across the 24-hr day and its evolution across gestation in women with type 1 diabetes who delivered an LGA (>90th centile) infant (represented by the dark wavy line) compared with those who did not (represented by the horizontal zero dotted line) with 95% pointwise Confidence Interval (gray section). The time period where the 95% Confidence Interval sit on the same side of 0.0, indicates a significant difference in glucose - for clarity these time periods have been illustrated as an example on Gestational week 11 by *, but this is not shown on the subsequent graphs.

Animation 1. Functional line fit showing the evolution of 24-hr mean CGM glucose profiles across gestation in women with type 1 diabetes. Mean glucose (mmol/L) and 95%

confidence interval by gestational age in weeks. The dotted horizontal line represents 7.8 mmol/L upper limit of recommended pregnancy target range.

Animation 2. Functional data analysis showing the differences in mean temporal glucose levels across the 24-hr day and its evolution across gestation in women with type 1 diabetes who gave birth to an LGA (>90th centile on GROW) infant (represented by the dark wavy line) compared with those who did not (represented by the horizontal zero dotted line) with 95% pointwise Confidence Interval (grey section). The time period where the 95% Confidence Interval sit on the same side of 0.0, indicates a significant difference in glucose.

Acknowledgements: The authors would like to thank all the women with type 1 diabetes who participated. We also acknowledge the invaluable support from the 31 clinical care teams and the CONCEPTT Steering Committee: Denice S Feig, Helen R Murphy, Elisabeth Asztalos, Jon F R Barrett, Rosa Corcoy, Alberto de Leiva, Lois E Donovan, J Moshe Hod, Lois Jovanovic, Erin Keely, Craig Kollman, Ruth McManus, Kellie E Murphy, Katrina Ruedy and George Tomlinson; and the antenatal diabetes clinical team at Skåne University Hospital and Östra/Sahlgrenska University Hospital in Sweden, in particular Anastasia Katsarou, Nael Shaat, Annika Dotevall, Verena Sengpiel, Anders Elfvin and Ulrika Sandgren; and the CGM data management team at the Parker Institute, Copenhagen, Denmark.

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 this data analysis. EMS and HRM designed this study. GRL performed the statistical data analysis. HRM, DF were responsible for CONCEPTT study design and data collection; KK,

KK, LEO, KB were responsible for the Swedish study design and data collection. Preliminary results were discussed with DF, KK and KB. EMS, HRM and GRL 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. DSF has received funds from Novo Nordisk for serving on an Expert Panel. GRL, DF, KK, KK, LEO and KB have no potential conflicts of interest relevant to this article.

Funding: The CONCEPTT trial was funded by Juvenile Diabetes Research Foundation (JDRF) grants #17-2011-533, and grants under the JDRF Canadian Clinical Trial Network, a public-private partnership including JDRF and FedDev Ontario and supported by JDRF #80-2010-585. Medtronic supplied the CGM sensors and CGM systems at reduced cost. GRL, EMS and HRM were part funded by HEFCE and MRC (MR/T001828/1). ES and HM were part funded by NIHR (EME 16/35/01), and HM was part funded by NIHR (CDF-2013-06-035). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the UK Department of Health. The Swedish study was funded by a research grant from Region Skåne, Sweden, and The Oak Foundation.

Data availability Data are available on request from the authors.

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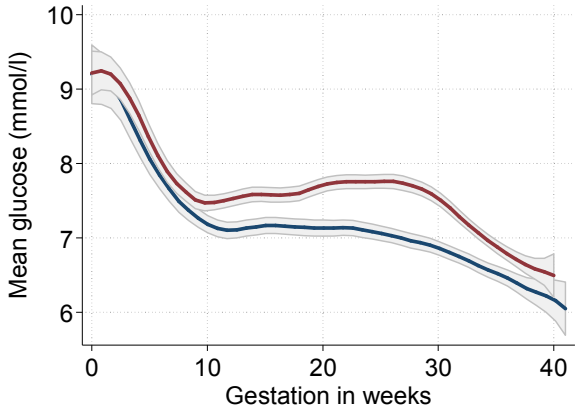
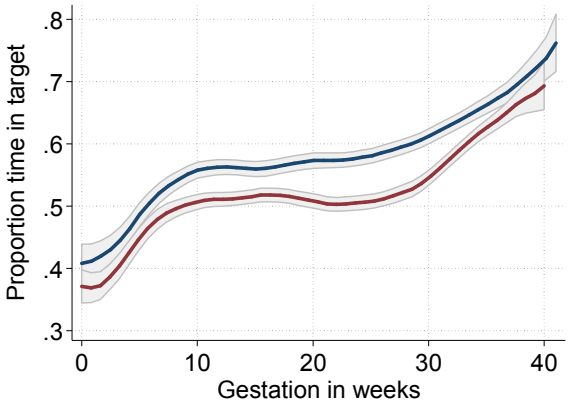
Figure 1. Evolution of CGM metrics (vertical axis) across gestation (horizontal axis) in women with type 1 diabetes. Women who delivered an LGA infant (>90th centile) (red line) are compared with those who did not (blue line). Each is fitted with a local polynomial smoothed curve and the 95% confidence interval is the shaded grey band. A) Mean CGM glucose; B) percentage of time spent in pregnancy target range TIR 3.5-7.8mmol/L (63-140mg/dL); C) percentage of time spent above pregnancy target range TAR >7.8 mmol/l (>140 mg/dL); D) percentage of time spent below target range TBR <3.5 mmol/L (<63 mg/dL); E) Coefficient of Variation; F) Mean Amplitude of Glucose Excursions (MAGE)

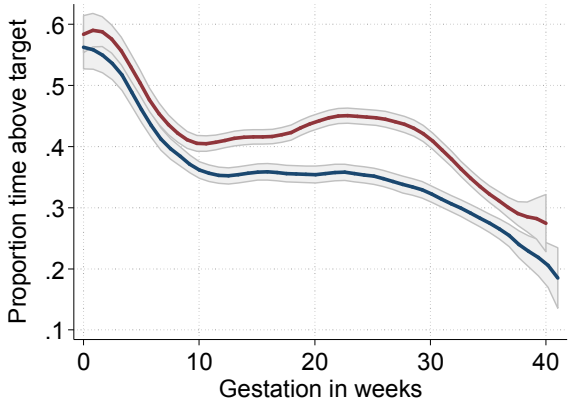
A) Mean glucose (mmol/l)



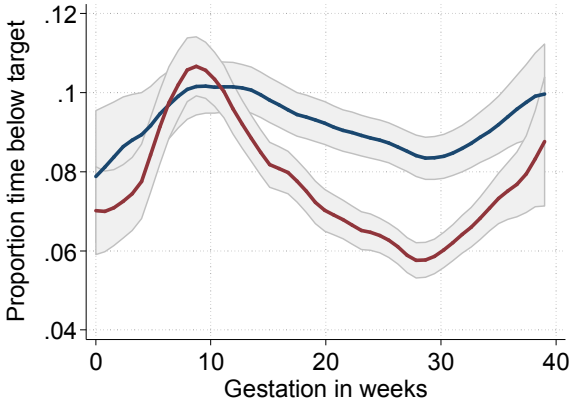
B) Percentage time in range (TIR) 3.5-7.8mmol/L [63-140mg/dL]



C) Percentage time above range (TAR) >7.8 mmol/L [>140mg/dL]

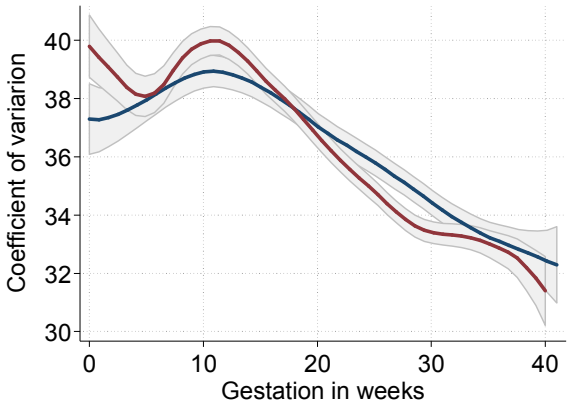


D) Percentage time below range (TBR) <3.5 mmol/L [<63mg/dL]



E) Coefficient of variation (%)

F) MAGE (mmol/L)


Coefficient of variarion
40
38
36
34
32
30
0
10
20
30
40
Gestation in weeks

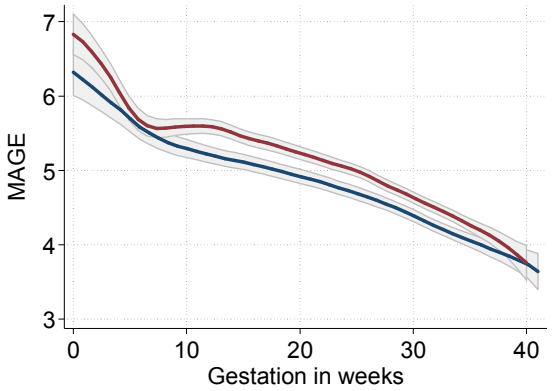
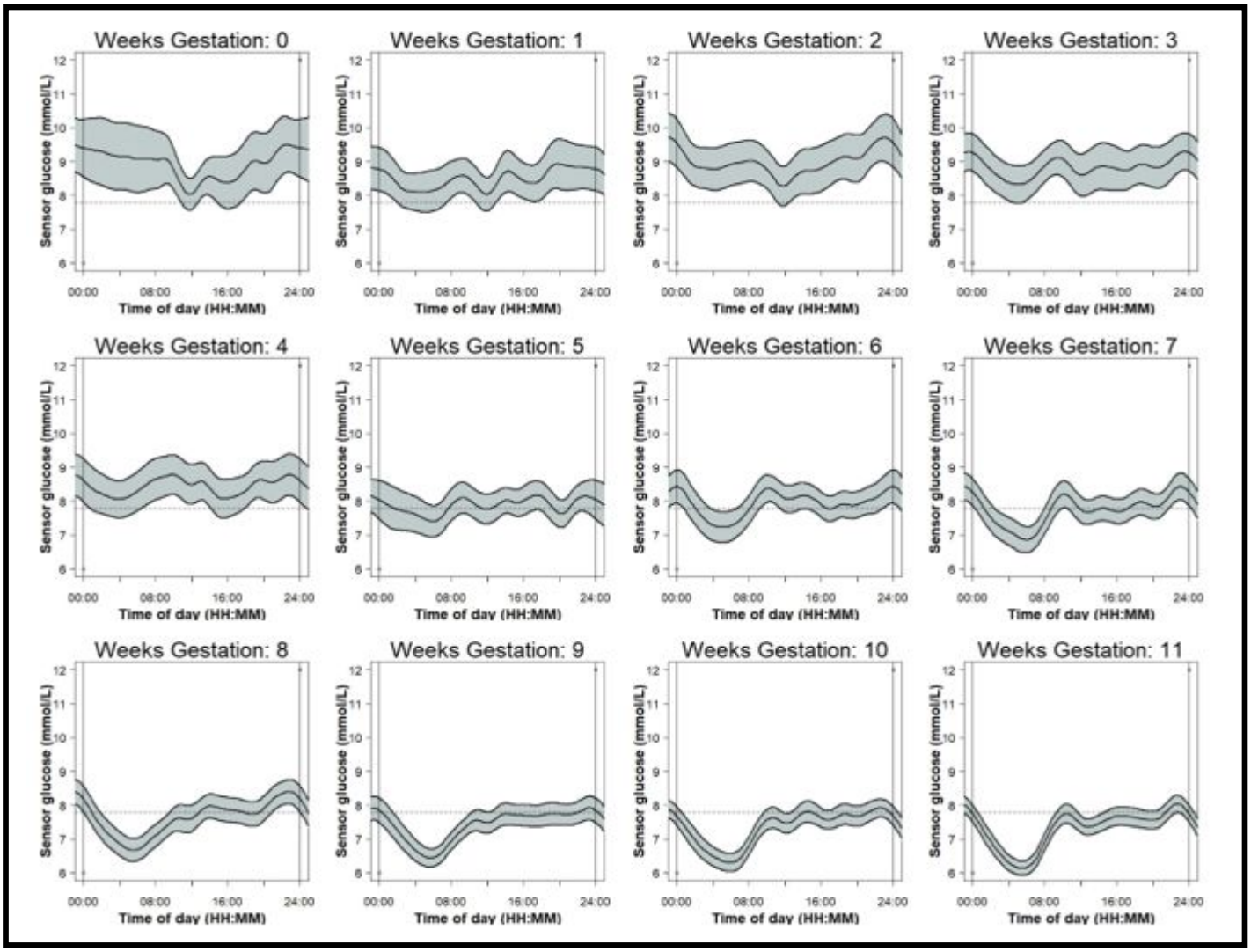
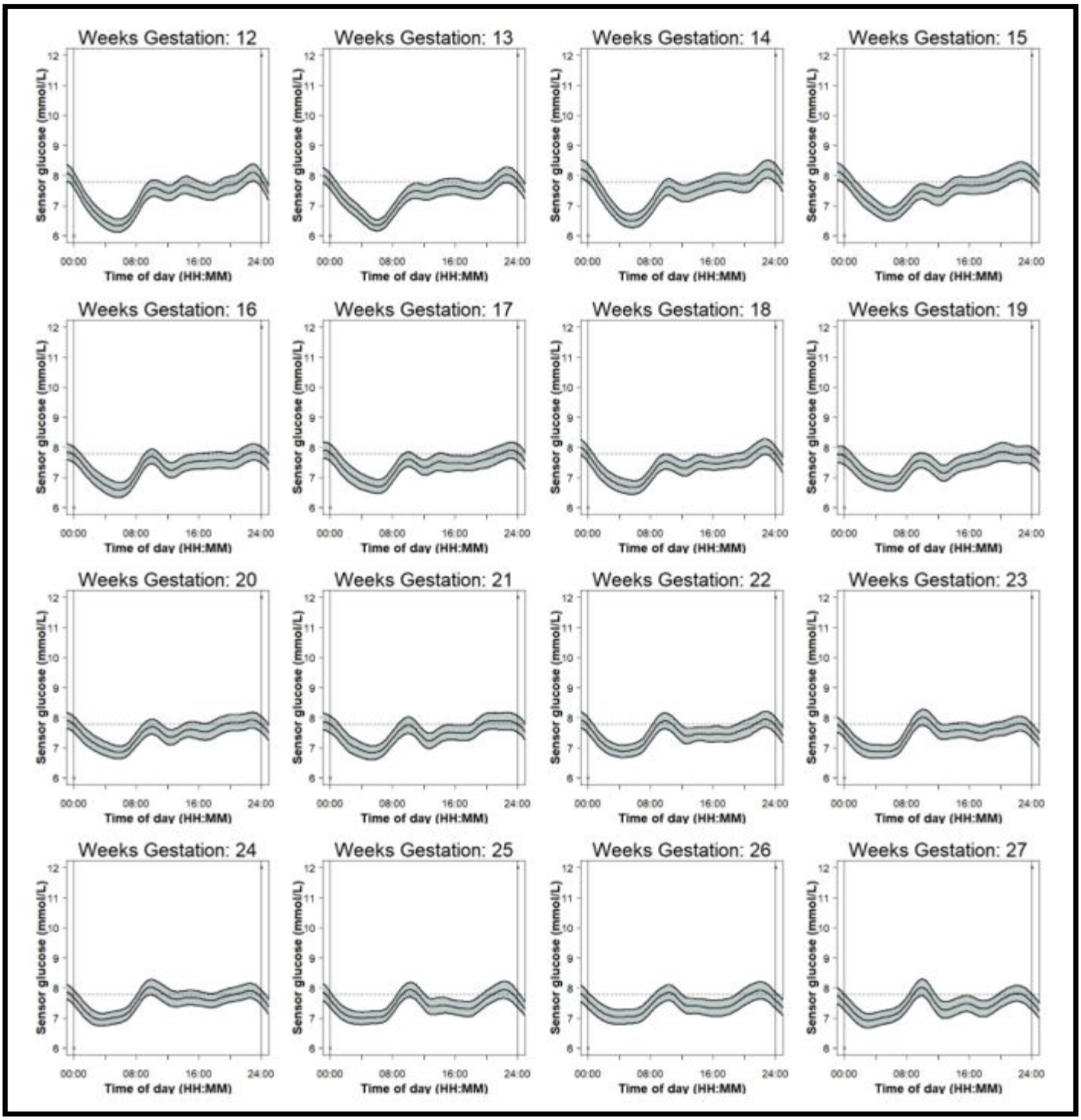

MAGE
7
6
5
4
3
0
10
20
30
40
Gestation in weeks

Figure 2. Functional line fit showing the evolution of 24-hour mean CGM glucose profiles across gestation in women with type 1 diabetes. Mean glucose (mmol/L) and 95% confidence interval by gestational age in weeks. The dotted horizontal line represents 7.8 mmol/L (140mg/dL) (upper limit of recommended target range for pregnancy).

Trimester 1



Trimester 2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Weeks Gestation: 13
Weeks Gestation: 14
Weeks Gestation: 15
Weeks Gestation: 16
Weeks Gestation: 17
Weeks Gestation: 18
Weeks Gestation: 19
Weeks Gestation: 20
Weeks Gestation: 21
Weeks Gestation: 22
Weeks Gestation: 23
Weeks Gestation: 24
Weeks Gestation: 25
Weeks Gestation: 26
Weeks Gestation: 27
Sensor glucose (mmol/L)
Time of day (HH:MM)
00:00
08:00
16:00
24:00
6
7
8
9
10
11
12

Trimester 3

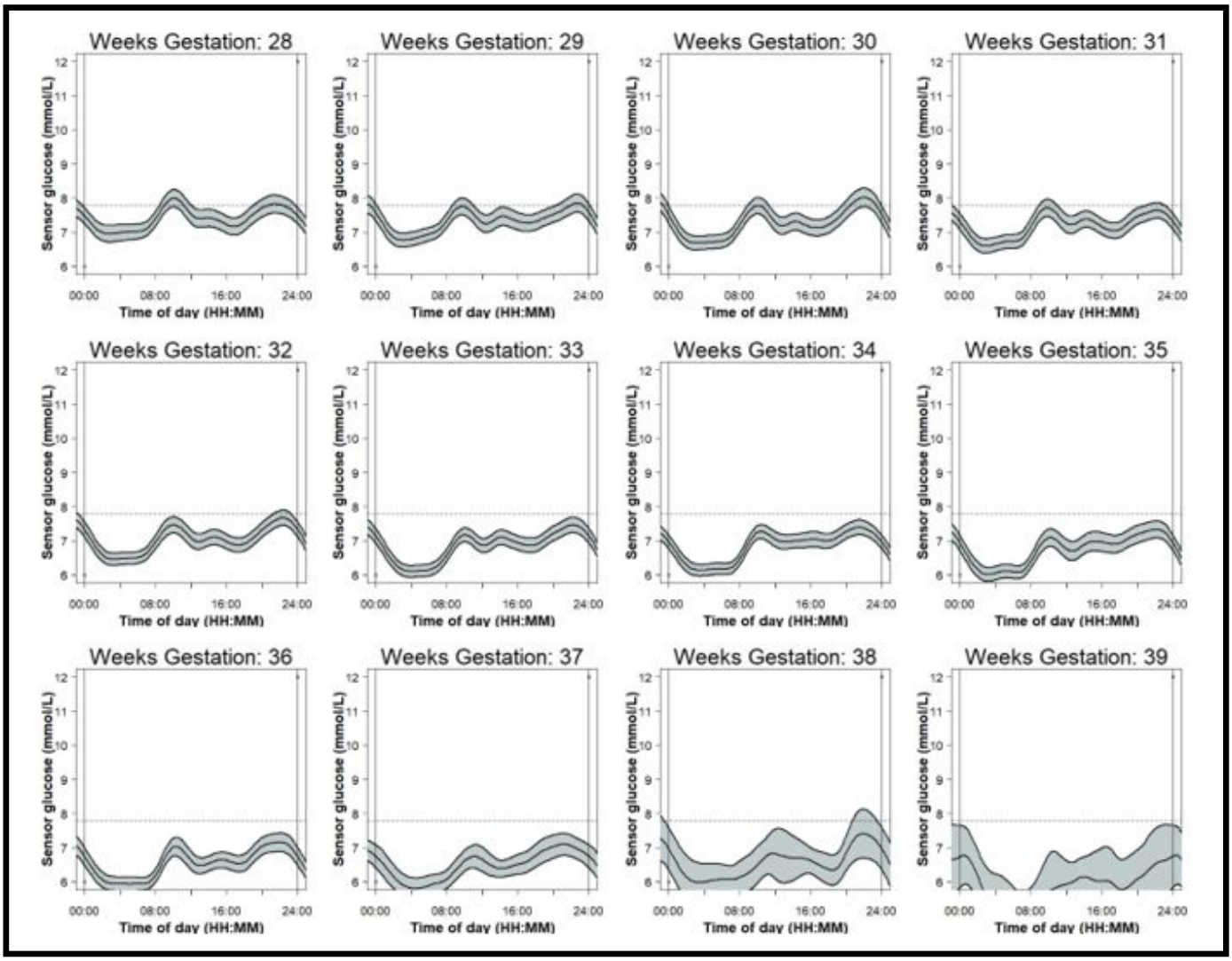
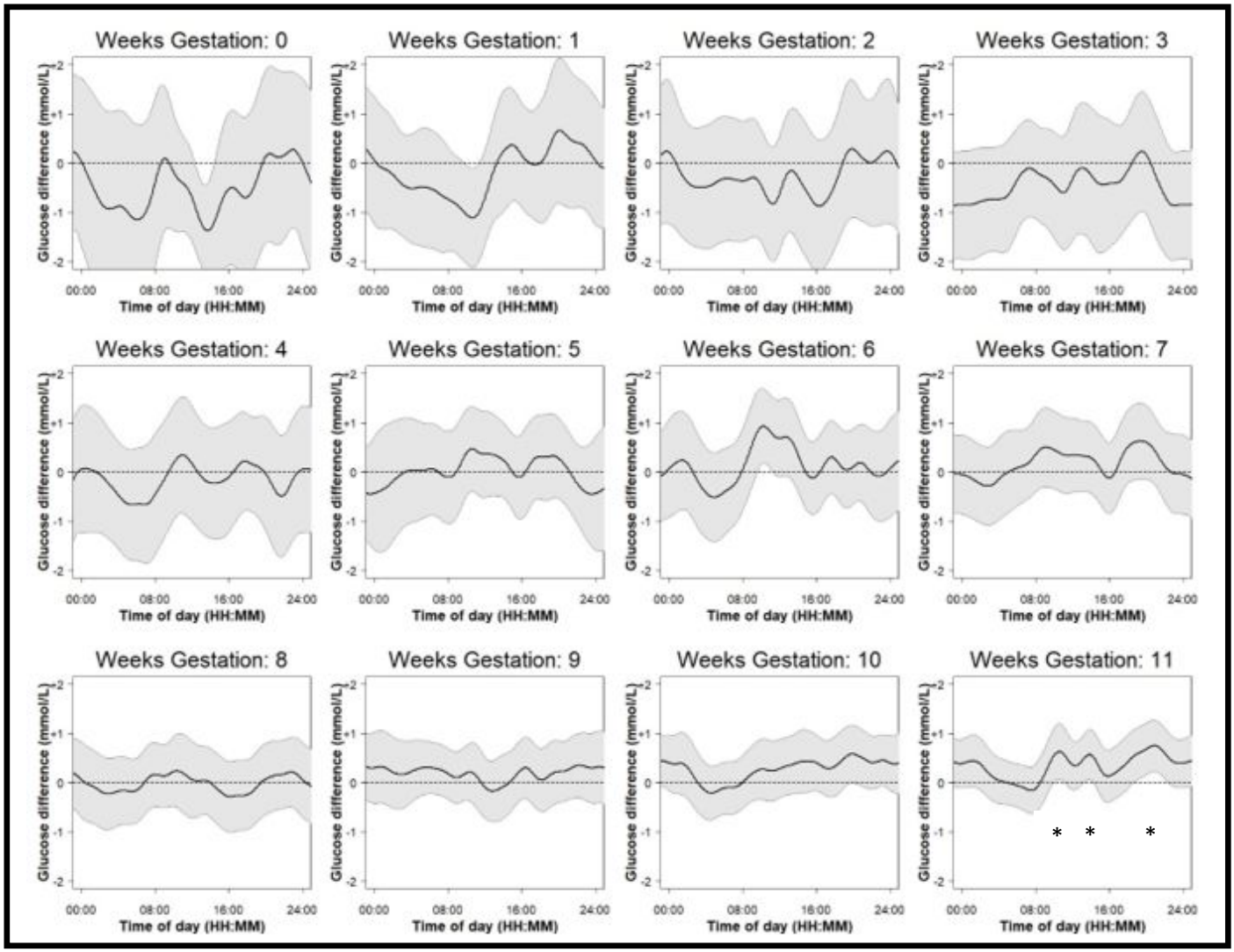
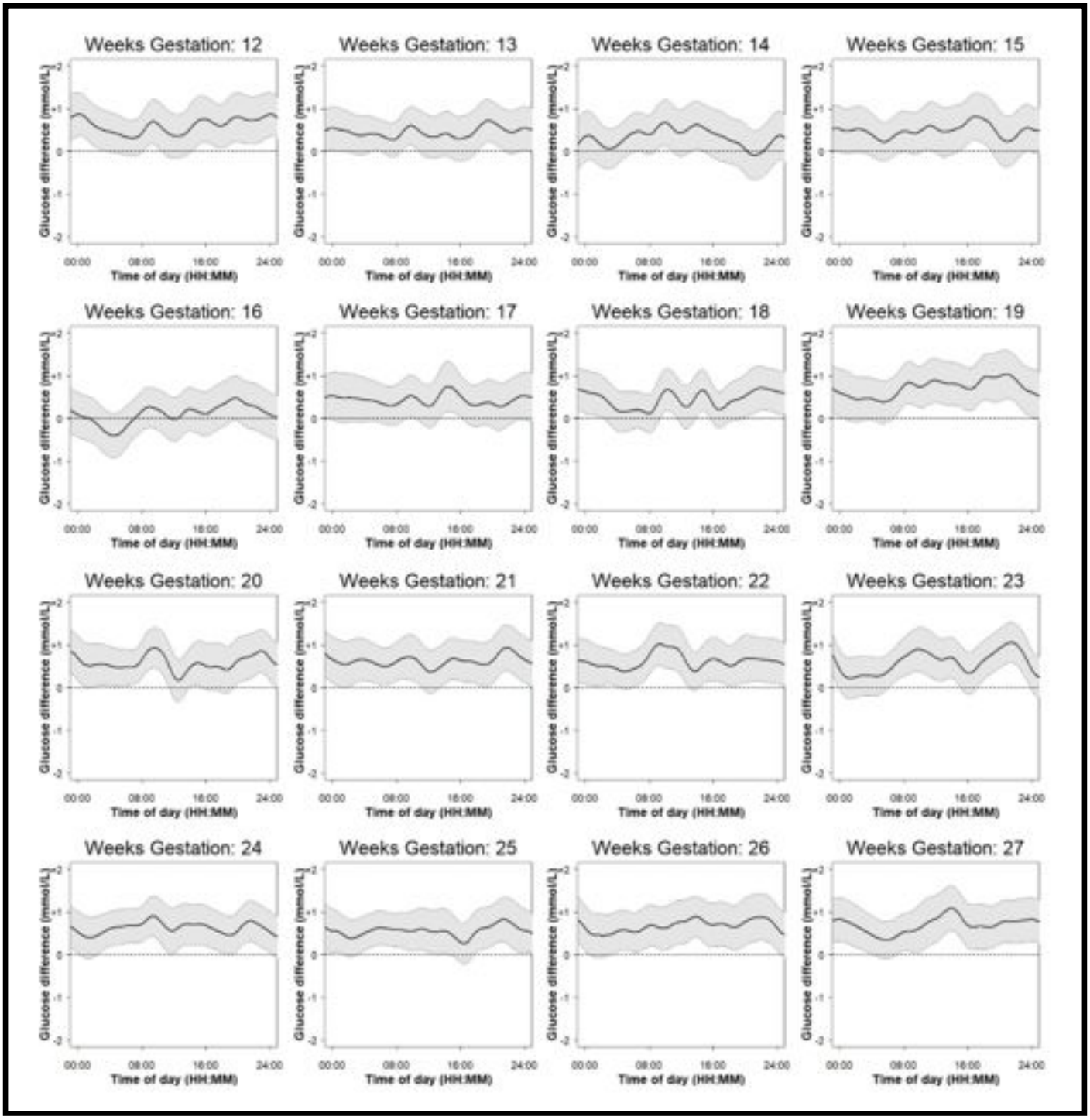

Weeks Gestation: 28
Weeks Gestation: 29
Weeks Gestation: 30
Weeks Gestation: 31
Weeks Gestation: 32
Weeks Gestation: 33
Weeks Gestation: 34
Weeks Gestation: 35
Weeks Gestation: 36
Weeks Gestation: 37
Weeks Gestation: 38
Weeks Gestation: 39
Sensor glucose (mmol/L)
Time of day (HH:MM)
00:00
08:00
16:00
24:00

Figure 3. Functional data analysis showing the differences in mean temporal glucose levels across the 24-hr day and its evolution across gestation in women with type 1 diabetes who delivered an LGA (>90th centile) infant (represented by the dark wavy line) compared with those who did not (represented by the horizontal zero dotted line) with 95% pointwise Confidence Interval (gray section). The time period where the 95% Confidence Interval sit on the same side of 0.0, indicates a significant difference in glucose - for clarity these time periods have been illustrated as an example on Gestational week 11 by *, but this is not shown on the subsequent graphs.

Trimester 1



Trimester 2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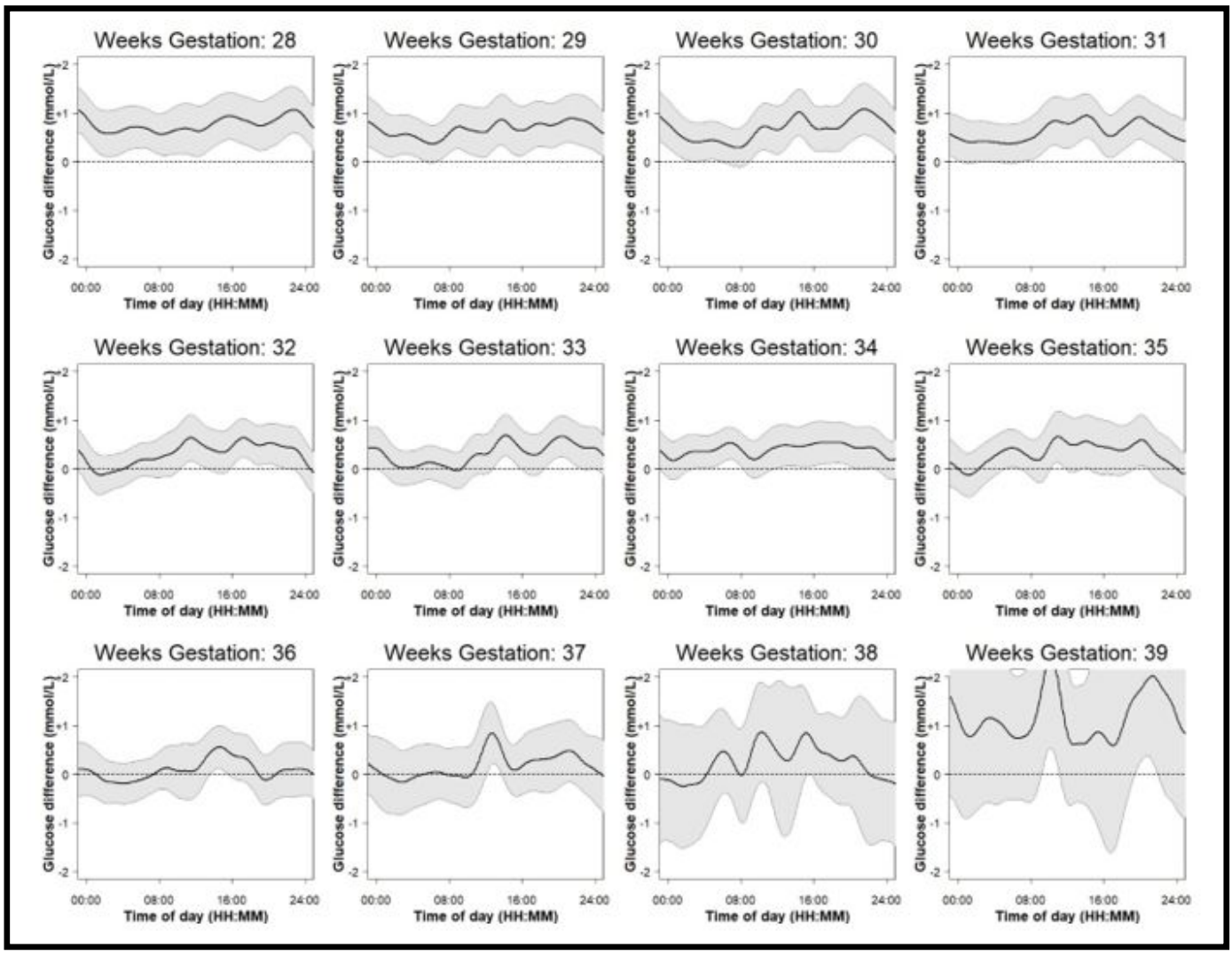
Weeks Gestation: 13
Weeks Gestation: 14
Weeks Gestation: 15
Weeks Gestation: 16
Weeks Gestation: 17
Weeks Gestation: 18
Weeks Gestation: 19
Weeks Gestation: 20
Weeks Gestation: 21
Weeks Gestation: 22
Weeks Gestation: 23
Weeks Gestation: 24
Weeks Gestation: 25
Weeks Gestation: 26
Weeks Gestation: 27
Glucose difference (mmol/L)
Time of day (HH:MM)

Trimester 3


Weeks Gestation: 28
Weeks Gestation: 29
Weeks Gestation: 30
Weeks Gestation: 31
Weeks Gestation: 32
Weeks Gestation: 33
Weeks Gestation: 34
Weeks Gestation: 35
Weeks Gestation: 36
Weeks Gestation: 37
Weeks Gestation: 38
Weeks Gestation: 39
Glucose difference (mmol/L)
Time of day (HH:MM)
00:00
08:00
16:00
24:00

Supplementary Appendix

Table S1: Total number of women with CGM glucose available for analysis for each gestational week

Gestational Week	Number of women
0	100
1	102
2	106
3	103
4	108
5	125
6	148
7	180
8	205
9	226
10	250
11	276
12	272
13	248
14	237
15	235
16	246
17	238
18	242
19	244
20	247
21	243
22	259
23	297
24	322
25	291
26	252
27	245
28	245
29	244
30	247
31	243
32	250
33	292
34	292
35	228
36	165
37	119
38	66
39	24