Suboptimal nocturnal glucose control is associated with large for gestational age in treated gestational diabetes

Authors: Graham R Law[1], Alia Alnaji[2], Lina Alrefaii[2], Del Endersby[3], Sarah J Cartland[2,3], Stephen G Gilbey[3], Paul E Jennings[4] Helen R Murphy[5], Eleanor M Scott[2,3]

(1) School of Health and Social Care, University of Lincoln, UK.

(2) Division of Clinical and Population Sciences, Leeds Institute of Cardiovascular and Metabolic Medicine , University of Leeds, UK

(3) Leeds Teaching Hospitals NHS Trust, Leeds, UK

(4) York NHS Foundation Trust, York, UK

(5) Division of Maternal Health, St Thomas's Hospital, Kings College London, UK

Corresponding author: Professor Eleanor M Scott, LIGHT Laboratories, Level 7, Clarendon Way, University of Leeds, Leeds, LS2 9JT; Tel: +44 (0)113 3437762; E-mail: e.m.scott@leeds.ac.uk

Word Count: Abstract: 248; Text: 2,758; Figures: 1; Tables: 2.

The authors' academic degrees are as follow: Graham R Law PhD, Alia Alnaji PhD, Lina Alrefaii MSc, Sarah J Cartland MB BS, Stephen G Gilbey MD, Paul E Jennings MD, Helen R Murphy MD, Eleanor M Scott MD.

Running title: Nocturnal glucose associated with large for gestational age

Abstract

Objective: Continuous glucose monitoring (CGM) provides far greater detail about fetal exposure to maternal glucose across the 24 hour day. Our aim was to examine the role of temporal glucose variation on the development of large for gestational age infants (LGA) in women with treated gestational diabetes (GDM).

Research Design and Methods: A prospective observational study of 162 pregnant women with GDM in specialist multidisciplinary antenatal diabetes clinics. Participants undertook a 7-day masked CGM at 30-32 weeks gestation. Standard summary indices and glycemic variability measures of CGM were calculated. Functional data analysis was applied to determine differences in temporal glucose profiles. LGA was defined as birth weight ≥90th percentile adjusted for infant sex, gestational age, maternal BMI, ethnicity and parity.

Results - Mean glucose was significantly higher in women who delivered an LGA infant (6.2 vs 5.8 mmol/l P=0.025 or 111.6 mg/dl vs 104.4 mg/dl respectively). There were no significant differences in percentage time in, above or below the target glucose range, or in glucose variability measures (all P>0.05). Functional data analysis revealed that the higher mean glucose was driven by a significantly higher glucose for 6 hours overnight (00h30-06h30) in mothers of LGA infants (6.0 ± 1.0 mmol/l vs 5.5 ± 0.8 mmol/l p=0.005; 108.0 ± 18.0 mg/dl vs 99.0 ± 14.4 mg/dl respectively).

Conclusions: Mothers of LGA infants run significantly higher glucose overnight compared to mothers without LGA. Detecting and addressing nocturnal glucose control may help to further reduce rates of LGA in women with GDM.

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

Introduction

Gestational diabetes mellitus (GDM) is the commonest medical disorder of pregnancy affecting 5-18% of all pregnancies (1-3). Periods of maternal hyperglycaemia stimulate fetal insulin secretion leading to fetal growth acceleration, fetal fat accumulation and large for gestational age (LGA) birthweights (4). LGA substantially increases the risk of preterm and instrumental delivery, caesarean section and stillbirth, and difficulties in delivery can lead to hypoxic brain damage, shoulder dystocia and permanent disability (5,6). Furthermore, infants born LGA are predisposed to developing obesity and type 2 diabetes perpetuating an intergenerational cycle of cardiometabolic disease (7,8). Optimising glucose control for the prevention of LGA is therefore considered important both for a successful pregnancy outcome may potentially benefit longer-term offspring health.

Current recommendations are that women with GDM should perform self-monitored blood glucose (SMBG) testing four times a day, with treatment adjusted to achieve fasting glucose targets of ≤ 5.3 mmol/l (≤ 95.4 mg/dl) and one-hour post meal glucose ≤7.8 mmol/l (≤ 140.4 mg/dl) (9,10). However, even women apparently achieving glycemic targets continue to deliver LGA infants (11,12). There are recognised limitations of the current approach to intermittently assessing capillary glucose levels. Firstly, the optimal time to post-prandial glucose peak varies according to the size and composition of the meal, and so SMBG at 1 or 2 hours can miss highest peak values (13,14). Secondly, between meal snacks which account for 20-25% of total daily energy intake are often not captured. Thirdly, overnight glucose

control overnight is not typically assessed. Thus, SMBG is unlikely to fully capture the complexity of day-to-day glucose excursions in pregnancy.

Continuous glucose monitoring (CGM) is increasingly accessible and accurate, providing far greater detail about fetal exposure to maternal glucose across the 24 hour day (15,16). We previously demonstrated that small differences in CGM glucose levels are associated with LGA in pregnant women with Type 1 and Type 2, pre-gestational diabetes (16,17). We have developed the application of functional data analysis (FDA) statistical techniques necessary to analyse time-series CGM data at a population level to maximise the temporal information obtained. In doing so we have been able to illustrate the time points across the 24 hour day where variations in glucose control differ in relation to LGA in Type 1 and 2 diabetes (16,18). The aim of the present study was therefore to examine whether CGM could be used to elucidate the role that temporal variation in glucose levels might play in the development of LGA in treated GDM pregnancies.

Research design and methods

Study design

This was a prospective observational cohort study of 162 pregnant women with GDM. After providing written informed consent, participants undertook a 7 day period of masked CGM at 30-32 weeks gestation. Maternal demographic and biomedical data was collected (age, ethnicity, parity, diabetes treatment, height, weight and BMI) at the start of pregnancy. At the end of the pregnancy the following obstetric and neonatal outcomes were recorded; gestational age at delivery, infant sex and birthweight. Customised birthweight centiles were calculated using the open source gestation network program GROW (GROW@perinatal.org)

(19) which adjusts for maternal height, weight, ethnicity, and parity; and for neonatal sex and gestational age. LGA was defined as infant birth weight on or above the 90th centile.

Study participants

Participants were aged between 18-45 years and had a singleton pregnancy. GDM was diagnosed using the UK NICE guideline criteria of fasting glucose ≥5.6 mmol/l (≥100.8 mg/dl) and/or 2 hour glucose ≥7.8 mmol/l (≥140.4 mg/dl) following a 75g oral glucose tolerance test at ~26 weeks gestation (11). All women were managed as per clinical guidelines (11,12) to achieve recommended SMBG targets (fasting ≤ 5.3 mmol/l (≤95.4 mg/dl); and one-hour post meal ≤ 7.8 mmol/l (≤140.4 mg/dl) prior to inclusion. Women were treated stepwise with diet and lifestyle as first-line therapy; with metformin and/or insulin as second-line therapy. Exclusion criteria included a physical or psychological disease likely to interfere with the conduct of the study, multiple pregnancy, non-English speaking.

Study oversight

The study was approved by the Yorkshire and Humber Regional Ethics Committee (13/YH/0268).

Continuous glucose monitoring (CGM)

The CGM device used was iPro2 (Medtronic) with Enlite sensor (Mean ARD 13.6%; Median ARD 10.1% (20). The CGM data obtained by the iPro2 was calibrated by simultaneous SMBG using approved and standardised blood glucose meters and test strips (Contour XL, Bayer), as per manufacturer's instructions. Data was downloaded via Medtronic CareLink, and exported for analysis. To make full use of the temporal information provided by the multiple measures of glucose recorded by CGM, data collected from each participant over the

length of time that each sensor was worn (mean 6.3 days) constituted a measurement episode. Morning fasting SMBG levels taken over the duration of the measurement episode were also collected.

Summary Statistical Analysis

We calculated the standard range of summary statistical indices (15-17, 21) including: mean CGM glucose levels; Area Under the Curve (AUC); the percentage of time spent within the pregnancy glucose target range (3.9-7.8 mmol/L; 70.2-140.4 mg/dl); time spent above (>7.8mmol/l; >140.4 mg/dl) and below (<3.9 mmol/l; <70.2 mg/dl) target range; low and high blood glucose index (LBGI; HBGI). Measures of glycemic variability; standard deviation (SD) and coefficient of variation (CV) of mean CGM glucose levels were calculated. The mean of the fasting SMBG levels were calculated. The difference in means was compared using a t-test.

Functional Data Analysis

Each of the glucose values recorded during each of the measurement episodes 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 (16,22). 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 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 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 Statistical Analysis

Multivariable regression analysis was used to establish the relationship between maternal glucose levels and LGA for the functional data analysis generated glucose function. We used a directed acyclic graph (www.dagitty.net) to determine the minimally sufficient dataset for estimating the direct effect of glucose on LGA. The model adjusted for maternal age, ethnicity, parity, maternal BMI, sex and gestational age of the infant as potential confounders in the relationship between glucose and birthweight centile. All statistical analyses were conducted in Stata (23) and R (24)

Results

CGM data were available for 162 women. Of these, 9 (5%) were excluded because of missing data or their CGM monitors had generated insufficient measurements (less than 72 hours). After excluding these participants, data from 153 singleton pregnancies, comprising 277,811 individual glucose measurements, conducted over 153 measurement episodes (mean of 151 hours/episode), were available for analyses. The participant characteristics of these women are shown in Table 1. There were no congenital anomalies, stillbirths or neonatal deaths in any of the participants. 14 (9%) participants delivered an infant with LGA, which is comparable to the expected background maternity population rate of 10%. The mean (SD) gestation at which CGM data was obtained was 31 ±1 weeks.

Summary Statistical Analysis

The summary statistical indices of CGM data, calculated separately for women who delivered LGA vs. non LGA infants are presented in Table 2. Mean CGM glucose was significantly higher in those women who subsequently delivered an LGA infant (6.2 ± 0.6 mmol/l vs 5.8 ± 0.6 mmol/l p=0.025; 111.6 ± 10.8 mg/dl vs 104.4± 10.8 mg/dl respectively). The mean nocturnal CGM glucose (00.00-06.00) was significantly higher in mothers of LGA infants (6.0 ± 1.0 mmol/l vs 5.5 ± 0.8 mmol/l p=0.005), with a peak glucose concentration reached at 02.00-03.00h. Mean daytime CGM glucose between 06.00 and 24.00 was slightly higher in mothers of LGA infants, but the between-group differences did not reach statistical significance (6.3 ± 0.6 mmol/l vs 6.0 ± 0.6 mmol/l p=0.058; 113.4 ± 10.8 mg/dl vs 108.0 ± 10.8 mg/dl respectively). There were no significant differences in any of the other standard summary CGM measures, including: time in, time above or time below target range, or glucose variability measures between women with and without LGA infants.

Mean fasting SMBG was not associated with LGA (5.3 ±1.0 mmol/l in LGA group, vs 5.2 ±0.8 mmol/l in non-LGA group p=0.219; 95.4 ± 18.0 mg/dl vs 93.6 ±14.4 mg/dl respectively)

Functional Data Analysis

Figure 1 summarises the temporal differences in glucose profile observed throughout the 24-hour day in women with LGA infants (as compared to women who did not have LGA infants) after applying functional data analysis to CGM data. Mothers who delivered LGA infants displayed significantly higher glucose levels during the night from 00h30-06h30 to those displayed by mothers who did not deliver LGA infants. There were no statistically significant differences observed in daytime glucose levels.

Conclusions

This is the first study to demonstrate, by analysis of CGM data, that women being treated for GDM who give birth to LGA infants, run significantly higher glucose concentrations for greater than six hours overnight compared to mothers who don't have LGA. As this period accounts for more than 25% of the 24 hour day this is a considerable period of time in which the fetus is, unintentionally, being exposed to higher maternal glucose concentrations, with the associated risk of LGA.

Current SMBG targets are focused on achieving fasting and postprandial glucose control during the day whilst awake (11,12). However, by only using these daytime targets, an opportunity to optimize glucose control overnight whilst asleep is being missed.

Although several studies have now explored CGM in GDM very few have examined the relationship to LGA. A study of 340 women with GDM , allocating 150 women to CGM and the rest to routine clinical care, found that those using CGM had significantly lower infant

birthweight (25) . Of the summary statistics calculated from a 24-hour snapshot of CGM data, only mean glucose concentration was associated with infant birthweight. A smaller study of 47 women with GDM with 85 hours of CGM performed at 28-32 weeks gestation found no relationship between glucose variability and birthweight, or pregnancy outcomes, but mean glucose was not reported (26). Together, these two studies support our findings suggesting that mean glucose concentration is more important in understanding increased fetal growth in GDM than standard glucose variability measures. Our study extends these findings by using functional data analysis, demonstrating that a higher mean glucose is predominantly being driven by suboptimal nocturnal glucose control with no significant difference in glucose during the day.

Having established that CGM is able to detect differences in glucose associated with LGA, it raises two questions pertinent to how this may be overcome: 1) What is causing the relative hyperglycemia overnight; and 2) Is there any evidence that using CGM helps to improve glucose control and reduce LGA?

A variety of factors are likely to be implicated in overnight hyperglycemia. These include the quantity and quality of carbohydrate and fat in the evening meal, eating later at night, and/or snacking before bedtime or during the nightIt may also reflect more sedentary behaviour, less physical activity and/or difficulty sleeping. Another potential explanation is increased hepatic glucose output whist fasting overnight, which may be particularly relevant for women who are overweight and/or obese. One of the limitations of this study is that the women were not asked to keep dietary logs or record the exact times at which they ate. Knowing the timing of meals and their composition could have allowed postprandial effects to be better isolated from the daytime exposure and might have offered a potential explanation for the higher nocturnal glucoses observed in the women giving birth to LGA infants.

Addressing whether CGM could be used as a potential intervention to improve nocturnal glycemia, the CONCEPTT study, a randomized controlled trial of real-time continuous CGM vs SMBG has firmly established the place of CGM in management of T1DM pregnancy, with small but significant changes in maternal glucose being associated with substantially reduced rates of LGA (17). However, there is less data on the benefit of CGM in GDM. There have been three interventional studies to-date. A study of 340 women with GDM, allocating 150 women to retrospective intermittent CGM (every 2-4 weeks) and the rest to routine SMBG showed lower risk of pre-eclampsia, caesarian section and lower infant birthweight in the CGM group (25). The GlucoMoms trial compared use of intermittent retrospective CGM (every 6 weeks) to SMBG in a mixed cohort of pregnant women with Type1 DM ,Type 2 DM and insulin-treated GDM (27). It did not show any between-group differences in LGA, although this was a heterogenous group, and was underpowered to detect whether women with GDM (with low rates of LGA) might benefit. A smaller randomized trial comparing intermittent retrospective CGM (at 28, 32 and 36 weeks gestation) to SMBG in 50 women with insulin-treated GDM, found that using CGM was associated with improved HbA1c at 37 weeks gestation but the study was also underpowered to detect differences in maternal-fetal outcomes (28). Whether CGM used throughout pregnancy is beneficial for reducing LGA in GDM still remains to be established. Given the low rates of LGA in treated GDM (generally <10%), a very large RCT would be required.

Another option, is to consider performing a period of CGM in women with well controlled GDM by SMBG targets, to help to identify those women who are at greatest risk of LGA. Based on our current data a mean glucose of ≥6 mmol/l (>108.0 mg/dl) overnight is associated with LGA and could indicate a need for further management/investigation. It is notable that CGM data from non-diabetic pregnancies suggests that mean overnight glucose in healthy pregnant women is ~ 4.6 mmol/l (82.8 mg/dl) (29). It is not currently known if

targeting nocturnal glucose control will improve LGA in GDM and this will require further investigation. However, it is known that small differences in glucose in pregnancy are reflected in clinical outcomes so this seems biologically plausible (17).

The strengths of this study are that it is a large, prospective study in an ethnically diverse population. It is thus highly representative of the women diagnosed with GDM in routine clinical care. By using customized growth centiles we adjusted for many of the factors influencing fetal growth. This is an improvement on studies that only adjust for infant sex and gestational age at birth, particularly when examining birthweight in an ethnically diverse population (19). 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 is also capable of recording glucose levels throughout both day and night without disrupting the normal activities of daily living (particularly periods of activity, rest and sleep). A further strength is that one week of CGM data was collected, contrary to most previous studies of CGM in GDM pregnancy, that have only used data obtained over 24-72 hours, making our data more representative. We acknowledge that recently published consensus guidelines, suggest that 2 weeks of CGM data are preferred although this recommendation is based on data outside of pregnancy (15).

The limitations of our study are that the women were diagnosed GDM based on the UK NICE criteria (11), which may represent a slightly different GDM population to that seen in international centers using different criteria (12). However, the women were well treated before undertaking CGM and had rates of LGA comparable to background population, so are likely to be reflective of treated GDM elsewhere (11,12). CGM data was only obtained at 30-32 weeks gestation, which may not be representative of glucose control at other times in pregnancy. However, the purpose of detecting maternal hyperglycemia is to allow time to

treat it effectively to reduce LGA prior to delivery. Thus, 32 weeks was a pragmatic time point to assess glucose control by CGM, as it was mid-way between diagnosis and delivery. This allowed time for treatment targets to be achieved and stable, yet with sufficient time left to further optimize treatment if necessary. We recognise that in common with many monitoring systems CGM has limitations, particularly with regard to the quality of glucose readings during rapid blood glucose changes and in situations of hypoglycaemia. The measurement of interstitial glucose may also not reflect precisely the levels of blood glucose.

In summary, nocturnal glucose control is currently overlooked in the management of gestational diabetes. Detecting and addressing nocturnal hyperglycemia may help to further reduce rates of large for gestational age infants in women with gestational diabetes.

Acknowledgements: The authors would like to thank all the pregnant women with GDM who participated. We also acknowledge the invaluable support from the diabetes antenatal care teams involved.

Contributors: GRL, EMS, AA, designed the study protocol. EMS, DE, AA, LA, PEJ, SGG, screened, enrolled and consented participants, provided antenatal clinical care and telephone support throughout the study. 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, HRM and EMS wrote the manuscript, which all authors critically reviewed.

Conflicts of Interest: EMS serves on Abbott Diabetes Care Global Advisory Panel and has received honoraria; HRM serves on the Medtronic European Scientific Advisory Board. GRL, AA, LA, DE, SJC, SGG, PEJ have no potential conflicts of interest relevant to this article.

Funding: GRL and EMS were funded by HEFCE. HM was funded by NIHR (CDF-2013-06-035). LA was funded by a Leeds University International Studentship. AA was funded by the Saudi Arabian Government. 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.

Provenance and peer review: Not commissioned; externally peer reviewed.

Table 1: Participant characteristics

	Total participants (N=153) Mean ± SD	LGA (N=14) Mean ± SD	Non-LGA (N=139) Mean ± SD
Age (years)	32.6 ± 5.4	31.4 ± 6.1	32.7 ± 5.4
BMI (Kg/m^2)	30.5 ± 6.0	32.1 ± 6.1	30.3 ± 6.0
Primiparous Multiparous	56 (36%) 97 (64%)	4 (29%) 0 (71%)	51 (38%) 84 (62%)
White European South Asian Afro-Caribbean Other	57% 22% 10% 11%	36% 43% 14% 7%	59% 20% 9% 12%
Gestation at birth (weeks)	38.4 ± 1.1	38.1 ± 0.9	38.8 ± 1.0
Birthweight (g)	3207 ± 487.8	3839 ±365.0	3144.1 ± 452.8
GROW birthweight centile (%)	42.2 ± 29.5	95.7 ± 2.5	36.8 ± 25.3
Diet alone Diet + Metformin Diet + Metformin + Insulin	70 (46%) 62 (40%) 21 (14%)	6 (43%) 7 (50%) 1 (7%)	64 (46%) 55 (40%) 20 (14%)

Table 2: Comparison of standard summary measures of CGM data and fasting SMBG amongst women who delivered LGA infants and those who did not. AUC= Area Under the Curve; LBGI= Low Blood Glucose Index; HBGI = High Blood Glucose Index; SD = standard deviation; CV = Coefficient of Variation.

	LGA (N=14) Mean (SD)	Non-LGA (N=139) Mean (SD)	P-value
Mean glucose(mmol/l)	6.2 (0.6)	5.8 (0.6)	**0.025**
Mean daytime glucose 06.00-24.00 (mmol/l)	6.3 (0.6)	6.0 (0.6)	0.058
Mean nocturnal glucose 00.00-06.00 (mmol/l)	6.0 (1.0)	5.5 (0.8)	**0.005**
AUC	448.0 (91.3)	442.9 (83.5)	0.828
Time in target range 3.9-7.8 mmol/l (%)	85 (9)	88 (11)	0.867
Time below 3.9 mmol/l (%)	2 (3)	4 (5)	0.804
Time above 7.8 mmol/l (%)	12 (9)	8 (1)	0.059
LBGI	1.1 (1.0)	1.6 (1.2)	0.909
HBGI	0.7 (0.5)	0.4 (0.6)	0.091
SD glucose (mmol/l)	1.2 (0.3)	1.1 (0.4)	0.118
CV glucose	19.6 (5.2)	18.7 (5.2)	0.278
Mean fasting SMBG (mmol/l)	5.3 (1.0)	5.2 (0.8)	0.219

Comparing the difference in means using a t test reporting the p value (bold for $p<0.05$).

Figure 1. Difference in mean temporal glucose levels across the 24 hour day, assessed by functional data analysis, between those mothers that go on to have an LGA infant (dark wavy line ⎯) and those mothers that do not (represented by horizontal zero dottedline - - - -) with 95% pointwise confidence intervals (grey section ▭). Significant differences using 95% CI's are highlighted by *. Dashed vertical lines represent 07.00 and 23.00.

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