Suboptimal Nocturnal Glucose Control Is Associated With Large for Gestational Age in Treated Gestational Diabetes Mellitus

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] and Eleanor M. Scott[2,3]

OBJECTIVE

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

RESEARCH DESIGN AND METHODS

We performed a prospective observational study of 162 pregnant women with GDM in specialist multidisciplinary antenatal diabetes clinics. Participants undertook 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). 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 h overnight (0030–0630 h) in mothers of LGA infants (6.0 ± 1.0 mmol/L vs. 5.5 ± 0.8 mmol/L, $P = 0.005$, and 108.0 ± 18.0 mg/dL vs. 99.0 ± 14.4 mg/dL).

CONCLUSIONS

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

[1]School of Health and Social Care, University of Lincoln, Lincoln, U.K.
[2]Division of Clinical and Population Sciences, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, U.K.
[3]Leeds Teaching Hospitals NHS Trust, Leeds, U.K.
[4]York NHS Foundation Trust, York, U.K.
[5]Division of Maternal Health, St Thomas' Hospital, King's College London, London, U.K.

Corresponding author: Eleanor M. Scott, e.m.scott@leeds.ac.uk

Gestational diabetes mellitus (GDM) is the commonest medical disorder of pregnancy, affecting 5–18% of all pregnancies (1–3). Periods of maternal hyperglycemia stimulate fetal insulin secretion, leading to fetal growth acceleration, fetal fat accumulation, and large for gestational age (LGA) birth weights (4). LGA substantially increases the risk of preterm and instrumental delivery, cesarean 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). Optimizing glucose control for the prevention of LGA is therefore considered important both for a successful pregnancy outcome and to 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 1-h postmeal glucose ≤7.8 mmol/L (≤140.4 mg/dL) (6,9). However, even women apparently achieving glycemic targets continue to deliver LGA infants (10,11). There are recognized limitations of the current approach to intermittently assessing capillary glucose levels. Firstly, the optimal time to postprandial glucose peak varies according to the size and composition of the meal, and so SMBG at 1 or 2 h can miss highest peak values (12,13). Secondly, between-meal snacks, which account for 20–25% of total daily energy intake, are often not captured. Thirdly, 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-h day (14,15). We previously demonstrated that small differences in CGM glucose levels are associated with LGA in pregnant women with type 1 and type 2, pregestational diabetes (15,16). We have developed the application of functional data analysis statistical techniques necessary to analyze time-series CGM data at a population level to maximize the temporal information obtained. In doing so, we have been able to illustrate the time points across the 24-h day where variations in glucose control differ in relation to LGA in type 1 and type 2 diabetes (15,17). The aim of the current 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 were 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 birth weight. Customized birth weight centiles were calculated using the open-source Gestation Network program GROW (GROW@perinatal .org) (18), which adjusts for maternal height, weight, ethnicity, and parity and for neonatal sex and gestational age. LGA was defined as infant birth weight ≥90th centile.

Study Participants
Participants were aged between 18 and 45 years and had a singleton pregnancy. GDM was diagnosed using the U.K. National Institute for Health and Care Excellence (NICE) guideline criteria of fasting glucose ≥5.6 mmol/L (≥100.8 mg/dL) and/or 2-h glucose ≥7.8 mmol/L (≥140.4 mg/dL) after a 75-g oral glucose tolerance test at ~26 weeks' gestation (10). All women were managed as per clinical guidelines (10,11) to achieve recommended SMBG targets (fasting ≤5.3 mmol/L [≤95.4 mg/dL] and 1-h postmeal ≤7.8 mmol/L [≤140.4 mg/dL]) prior to inclusion. Women were treated stepwise with diet and lifestyle as first-line therapy and with metformin and/or insulin as second-line therapy. Exclusion criteria included having a physical or psychological disease likely to interfere with the conduct of the study, multiple pregnancy, and not speaking English.

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

CGM
The CGM device used was iPro2 (Medtronic) with the Enlite Sensor (mean absolute relative difference 13.6% and median absolute relative difference 10.1%) (19). The CGM data obtained by the iPro2 were calibrated by simultaneous SMBG using approved and standardized blood glucose meters and test strips (Contour XT; Bayer) per the manufacturer's instructions. Data were downloaded via CareLink (Medtronic) 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 (14–16,20) including mean CGM glucose levels, area under the curve, 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 (>7.8 mmol/L [>140.4 mg/dL]) and below (<3.9 mmol/L [<70.2 mg/dL]) target range, and low and high blood glucose indices. Measures of glycemic variability and SD and coefficient of variation of mean CGM glucose levels were calculated. The mean of the fasting SMBG levels was 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 5 min throughout that measurement episode. These trajectories were modeled using the technique of fitting B-splines to the repeated measures (15,21). 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-h 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-min intervals over each 24-h measurement period, with data from measurements recorded during the 4 h either side of midnight (i.e., from 2000 to 0400 h) repeated at the beginning and end to eliminate artifactual 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 data set 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 birth weight centile. All statistical analyses were conducted in Stata (22) and R (23).

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 (<72 h). After exclusion of these participants, data from 153 singleton pregnancies, comprising 277,811 individual glucose measurements, conducted over 153 measurement episodes (mean of 151 h/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. Fourteen (9%) participants delivered an infant with LGA, which is comparable with the expected background maternity population rate of 10%. The mean ± SD gestation at which CGM data were obtained was 31 ± 1 weeks.

Summary Statistical Analysis

The summary statistical indices of CGM data, calculated separately for women who delivered LGA versus non-LGA infants, are presented in Table 2. Mean

CGM glucose was significantly higher in women who subsequently delivered an LGA infant (6.2 ± 0.6 mmol/L vs. 5.8 ± 0.6 mmol/L, $P = 0.025$, and 111.6 ± 10.8 mg/dL vs. 104.4 ± 10.8 mg/dL). The mean nocturnal CGM glucose (0000–0600 h) 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 0200–0300 h. Mean daytime CGM glucose between 0600 and 2400 h 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, $P = 0.058$, and 113.4 ± 10.8 mg/dL vs. 108.0 ± 10.8 mg/dL). 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 women 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, $P = 0.219$, and 95.4 ± 18.0 mg/dL vs. 93.6 ± 14.4 mg/dL).

Functional Data Analysis

Figure 1 summarizes the temporal differences in glucose profile observed throughout the 24-h day in women with LGA infants (compared with women who did not have LGA infants) after application of functional data analysis to CGM data. Mothers who delivered LGA infants displayed significantly higher glucose levels during the night from 0030 to 0630 h compared with 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 >6 h overnight compared with mothers who do not have LGA infants. As this period accounts for $>25\%$ of the 24-h 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 while patients are awake (10,11). However, with use of only these daytime targets, an opportunity to optimize glucose control overnight while asleep is being missed.

Although several studies have now explored CGM in GDM, very few have examined the relationship with LGA. A study of 340 women with GDM, allocating 150 women to CGM and the rest to routine clinical care, found that infants of those using CGM had significantly lower birth weight (24). Of the summary statistics calculated from a 24-h snapshot of CGM data, only mean glucose concentration was associated with infant birth weight. A smaller study of 47 women with GDM with 85 h of CGM performed at 28–32 weeks' gestation found no relationship between glucose variability and birth weight, or pregnancy outcomes, but mean glucose was not reported (25). Together, these two studies support our findings suggesting that mean glucose concentration is more important in understanding increased fetal growth in GDM than are 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, we raise 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, or snacking before bedtime or during the night. It may also reflect more sedentary behavior, less physical activity, or difficulty sleeping. Another potential explanation is increased hepatic glucose output while 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

Table 1—Participant characteristics

	Total participants (N = 153)	LGA (N = 14)	Non-LGA (N = 139)
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	56 (36)	4 (29)	51 (38)
Multiparous	97 (64)	10 (71)	84 (62)
Ethnicity (%)			
White European	57	36	59
South Asian	22	43	20
Afro-Caribbean	10	14	9
Other	11	7	12
Gestation at birth (weeks)	38.4 ± 1.1	38.1 ± 0.9	38.8 ± 1.0
Birth weight (g)	3,207 ± 487.8	3,839 ± 365.0	3,144.1 ± 452.8
GROW birth weight centile (%)	42.2 ± 29.5	95.7 ± 2.5	36.8 ± 25.3
Diet alone	70 (46)	6 (43)	64 (46)
Diet + metformin	62 (40)	7 (50)	55 (40)
Diet + metformin + insulin	21 (14)	1 (7)	20 (14)

Data are means ± SD or n (%) unless otherwise indicated.

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 glucose levels observed in the women giving birth to LGA infants.

Addressing whether CGM could be used as a potential intervention to improve nocturnal glycemia, the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT), a randomized controlled trial of real-time continuous CGM versus SMBG, has firmly established the place of CGM in management of pregnancy involving type 1 diabetes, with small but significant changes in maternal glucose being associated with substantially reduced rates of LGA (16). However, there are 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 preeclampsia and caesarian section and lower infant birth weight in the CGM group (24). The GlucoMoms trial compared use of intermittent retrospective CGM (every 6 weeks) to SMBG in a mixed cohort of pregnant women with type 1 diabetes, type 2 diabetes, and insulin-treated GDM (26). 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) with SMBG in 50 women with insulin-treated GDM found that using CGM was associated with improved HbA$_{1c}$ at 37 weeks' gestation, but the study was also underpowered to detect differences in maternal-fetal outcomes (27). 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 randomized controlled trial would be required.

Another option is to consider performing CGM for a period in women with well-controlled GDM using 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 pregnancies without diabetes suggest that mean overnight glucose in healthy pregnant women is ~4.6 mmol/L (82.8 mg/dL) (28). It is not currently known whether targeting nocturnal glucose control will improve LGA in GDM, and this will

Table 2—Comparison of standard summary measures of CGM data and fasting SMBG among women who delivered LGA infants and those who did not

	LGA (N = 14)	Non-LGA (N = 139)	P
Glucose (mmol/L)	6.2 ± 0.6	5.8 ± 0.6	**0.025**
Daytime glucose 0600–2400 h (mmol/L)	6.3 ± 0.6	6.0 ± 0.6	0.058
Nocturnal glucose 0000–0600 h (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 <3.9 mmol/L	2 ± 3	4 ± 5	0.804
% time <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
Fasting SMBG (mmol/L)	5.3 ± 1.0	5.2 ± 0.8	0.219

Data are means ± SD. AUC, area under the curve; CV, coefficient of variation; HBGI, high blood glucose index; LBGI, low blood glucose index. Comparing the difference in means using a t test reporting the P value (boldface type for P < 0.05).
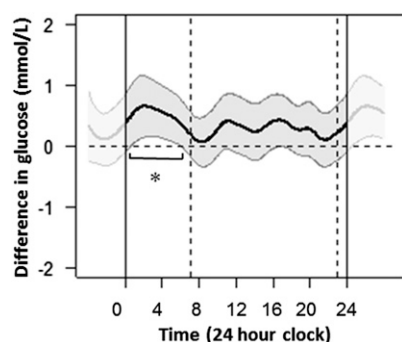
Figure 1—Difference in mean temporal glucose levels across the 24-h day, assessed by functional data analysis, between those mothers that go on to have an LGA infant (dark wavy line) and those mothers who do not (represented by horizontal zero dotted line) with 95% pointwise CIs (gray section). *Significant differences using 95% CIs. Dashed vertical lines represent 0700 and 2300 h.

require further investigation. However, it is known that small differences in glucose in pregnancy are reflected in clinical outcomes, so this seems biologically plausible (16).

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 birth weight in an ethnically diverse population (18). 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 HbA$_{1c}$. 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 CGM data were collected for 1 week, contrary to most previous studies of CGM in GDM pregnancy that have only used data obtained over 24–72 h, 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 (14).

The limitations of our study are that the women were diagnosed with GDM

based on the U.K. NICE criteria (10), so our study population may represent a slightly different GDM population compared with those seen in international centers using different criteria (11). However, the women were well treated before undertaking CGM and had rates of LGA comparable with the background population and so are likely to be reflective of women with treated GDM elsewhere (10,11). CGM data were 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 midway 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 recognize 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 hypoglycemia. 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 GDM. Detecting and addressing nocturnal hyperglycemia may help to further reduce rates of LGA infants in women with GDM.

References

1. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
2. O'Sullivan EP, Avalos G, O'Reilly M, Dennedy MC, Gaffney G, Dunne F; Atlantic DIP Collaborators. Atlantic Diabetes in Pregnancy (DIP): the prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. Diabetologia 2011;54:1670–1675
3. Coustan DR, Lowe LP, Metzger BE, Dyer AR; International Association of Diabetes and Pregnancy Study Groups. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol 2010;202:654.e1–654.e6
4. Langer O, Rodriguez DA, Xenakis EM, McFarland MB, Berkus MD, Arrendondo F. Intensified versus conventional management of gestational diabetes. Am J Obstet Gynecol 1994; 170:1036–1046; discussion 1046–1047
5. Lim JH, Tan BC, Jammal AE, Symonds EM. Delivery of macrosomic babies: management and outcomes of 330 cases. J Obstet Gynaecol 2002;22:370–374
6. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
7. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol 2007;165:849–857
8. Geserick M, Vogel M, Gausche R, et al. Acceleration of BMI in early childhood and risk of sustained obesity. N Engl J Med 2018;379:1303–1312
9. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes mellitus: falling through the net. Diabetologia 2015;58:2003–2012
10. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period [Internet], 2015. Available from www.nice.org.uk/guidance/ng3. Accessed 9 January 2018
11. American Diabetes Association. 13. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S137–S143

12. Jovanovic L. Continuous glucose monitoring during pregnancy complicated by gestational diabetes mellitus. Curr Diab Rep 2001;1:82–85

13. Kestilä KK, Ekblad UU, Rönnemaa T. Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. Diabetes Res Clin Pract 2007; 77:174–179

14. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40: 1631–1640

15. Law GR, Ellison GTH, Secher AL, et al. Analysis of continuous glucose monitoring in pregnant women with diabetes: distinct temporal patterns of glucose associated with large-for-gestational-age infants. Diabetes Care 2015;38: 1319–1325

16. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390: 2347–2359

17. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. N Engl J Med 2016; 375:644–654

18. Gardosi J, Francis A, Turner S, Williams M. Customized growth charts: rationale, validation and clinical benefits. Am J Obstet Gynecol 2018; 218(2S):S609–S618

19. Bailey TS, Ahmann A, Brazg R, et al. Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor. Diabetes Technol Ther 2014;16:277–283

20. Hernandez TL, Barbour LA. A standard approach to continuous glucose monitor data in pregnancy for the study of fetal growth and infant outcomes. Diabetes Technol Ther 2013;15: 172–179

21. Ramsay JO, Hooker G, Graves S. *Functional Data Analysis with R and MATLAB.* New York, Springer-Verlag, 2009

22. StataCorp. *Stata Statistical Software: Release 12*. College Station, TX, StataCorp LP, 2011

23. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2008

24. Yu F, Lv L, Liang Z, et al. Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: a prospective cohort study. J Clin Endocrinol Metab 2014;99:4674–4682

25. Panyakat WS, Phatihattakorn C, Sriwijitkamol A, Sunsaneevithayakul P, Phaophan A, Phichitkanka A. Correlation between third trimester glycemic variability in non-insulin-dependent gestational diabetes mellitus and adverse pregnancy and fetal outcomes. J Diabetes Sci Technol 2018;12: 622–629

26. Voormolen DN, DeVries JH, Sanson RME, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial. Diabetes Obes Metab 2018;20:1894–1902

27. Paramasivam SS, Chinna K, Singh AKK, et al. Continuous glucose monitoring results in lower HbA_{1c} in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. Diabet Med 2018;35:1118–1129

28. Harmon KA, Gerard L, Jensen DR, et al. Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. Diabetes Care 2011;34:2198–2204