Analysis of Continuous Glucose Monitoring in Pregnant Women With Diabetes: Distinct Temporal Patterns of Glucose Associated With Large-for-Gestational-Age Infants

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OBJECTIVE

Continuous glucose monitoring (CGM) is increasingly used to assess glucose control in diabetes. The objective was to examine how analysis of glucose data might improve our understanding of the role temporal glucose variation has on large-for-gestational-age (LGA) infants born to women with diabetes.

RESEARCH DESIGN AND METHODS

Functional data analysis (FDA) was applied to 1.68 million glucose measurements from 759 measurement episodes, obtained from two previously published randomized controlled trials of CGM in pregnant women with diabetes. A total of 117 women with type 1 diabetes (n = 89) and type 2 diabetes (n = 28) who used repeated CGM during pregnancy were recruited from secondary care multidisciplinary obstetric clinics for diabetes in the U.K. and Denmark. LGA was defined as birth weight ≥90th percentile adjusted for sex and gestational age.

RESULTS

A total of 54 of 117 (46%) women developed LGA. LGA was associated with lower mean glucose (7.0 vs. 7.1 mmol/L; P < 0.01) in trimester 1, with higher mean glucose in trimester 2 (7.0 vs. 6.7 mmol/L; P < 0.001) and trimester 3 (6.5 vs. 6.4 mmol/L; P < 0.01). FDA showed that glucose was significantly lower midmorning (0900–1100 h) and early evening (1900–2130 h) in trimester 1, significantly higher early morning (0330–0630 h) and throughout the afternoon (1130–1700 h) in trimester 2, and significantly higher during the evening (2030–2330 h) in trimester 3 in women whose infants were LGA.

CONCLUSIONS

FDA of CGM data identified specific times of day that maternal glucose excursions were associated with LGA. It highlights trimester-specific differences, allowing treatment to be targeted to gestational glucose patterns.

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Globally, diabetes affects up to 12% of all pregnancies (1), and the proportion of pregnancies affected is increasing (2). Among women with pregestational (type 1 or 2) diabetes, macrosomia, or large for gestational age (LGA), is the commonest complication of pregnancy, affecting one in two infants (3–8). As well as the adverse obstetric (labor complications, perineal tearing, instrumental delivery, and caesarean section) and perinatal (shoulder dystocia, respiratory distress, neonatal hypoglycemia, and stillbirth) outcomes associated with LGA, LGA infants are themselves at increased risk of developing obesity, diabetes, and cardiovascular disease in later life (9–13).

Maternal hyperglycemia has long been considered the principal determinant of LGA and the factor most amenable to intervention (14,15). However, the prevalence of LGA remains high even in diabetic pregnancies that are considered clinically "well controlled" where self-monitored capillary blood glucose (SMBG) or HbA$_{1c}$ measurements indicate that clinical management has been successful in normalizing maternal glucose levels (4–6,16). This suggests either that something other than glucose levels is responsible for LGA in these women or that SMBG and HbA$_{1c}$ measurements fail to detect the variation in glucose levels that is capable of causing LGA.

This has led to substantial interest in the potential role that continuous glucose monitoring (CGM) might play in improving the clinical assessment and management of glycemic control. Nonetheless, the sheer volume of data these devices produce (288 glucose measurements per day) and the complexity of the underlying signals these data contain mean that CGM data have proved challenging to analyze and interpret. To address this, some analysts have recommended using a wide range of summary statistical indices (such as calculating average glucose levels over specified time periods or measuring the time above, below, or within a specified target) (17). Unfortunately, all of these indices remove much of the potential additional information that such temporal data offer. This includes not only an indication of glucose levels at or across specific points in time but also measures of change (or velocity), rate of change (or acceleration), and variability. Accessing

this additional information, and making it available for clinical interpretation and application, requires more sensitive statistical techniques. Functional data analysis (FDA) is one such technique, being capable of summarizing temporal trends in continuously recorded measurements in a form that is amenable to subsequent multivariable statistical analysis. The aim of the current study was therefore to examine the extent to which summary statistical indices and FDA of CGM data might improve our understanding of the role that residual variation in glucose levels might play in the development of LGA infants in clinically well-controlled diabetic pregnancies.

RESEARCH DESIGN AND METHODS

This multicenter study drew on data from two studies: one based in England (East Anglia) and the second in Denmark (Copenhagen) (16,18). Both studies recruited pregnant women with pregestational type 1 or type 2 diabetes to prospective, randomized controlled trials that explored the clinical impact of CGM on maternal, fetal, and neonatal health outcomes. All participants were treated with insulin either before pregnancy or as soon as pregnancy was confirmed.

In England, pregnant participants, aged 16–45 years, were recruited in two secondary care diabetes antenatal clinics between 2003 and 2006. In Denmark, pregnant participants, aged 19–43 years, were recruited from one diabetes antenatal clinic between 2009 and 2011. Full details of clinical recruitment procedures (including the exclusion of participants with severe medical or psychological comorbidities) have been described previously (16,18).

Antenatal and Perinatal Care

All participants received routine clinical care as per national guidelines. In England, this involved antenatal clinic visits every 2–4 weeks, four to six of which included additional study-related assessments. In Denmark, antenatal clinic visits occurred every 2 weeks, with five study visits undertaken at 8, 12, 21, 27, and 33 weeks gestation. Both studies used comparable glucose targets: in England <5.5 mmol/L before meals, <7.8 mmol/L at 60 min, and <6.7 mmol/L at 120 min postmeals; and in Denmark 4.0–6.0 mmol/L before meals, 4.0–8.0 mmol/L at 90 min postmeal, and 6.0–8.0 mmol/L before bed.

Antenatal records provided data on the following: maternal BMI, HbA$_{1c}$ levels, age at onset of diabetes, type of diabetes, insulin regimen (i.e., via pump or multiple daily injections), infant sex, birth weight, and gestational age at birth. The latter were used to define LGA as a birth weight on or above the 90th percentile for sex- and gestation-adjusted birth weight according to British (19) and Scandinavian (20) growth references.

CGM

Continuous glucose monitors were used to record electrochemically measured subcutaneous interstitial glucose concentrations every 5 min, generating 288 measurements per day. Both studies used Medtronic CGM systems (Medtronic-MiniMed, Northridge, CA), with CGM-Gold sensors used in England and Guardian Real-Time CGM with Sof-Sensors in Denmark. Monitors were calibrated against capillary blood glucose measurements as per the manufacturer's instructions. To make full use of the temporal information provided by the multiple measures of glucose recorded by CGM, data collected from each participant over a series of days were taken to constitute a measurement episode. In England, these episodes constituted the length of time that each sensor was worn (5–7 days). In Denmark, these measurement episodes comprised separate weeks. Based on the volume of CGM data available, our analyses have 98% power at the 5% level to detect a 1 mmol/L difference in glucose between participants who delivered infants with or without LGA.

Summary Statistical Analysis

To facilitate comparisons between the CGM data examined in this and previous studies, we calculated a range of summary statistical indices including the following: mean CGM glucose levels; the percentage of time spent within the diabetes pregnancy glucose target range (3.5–7.8 mmol/L); and the area under the curve (a measure of participant exposure to high, low, and normal glucose levels over time) for all glucose measurements that exceeded thresholds of 7.8 or 6.7 mmol/L, or fell below thresholds of 3.5 or 2.8 mmol/L (17,21). Measures of glycemic variability were also calculated (22), including the following: SD of mean CGM glucose levels, which shows how much variation there is from

the average; M-value (23), which is a measure of variability, calculated using a formula from each glucose value, and then divided by the total number of glucose values to produce a mean; mean amplitude of (positive + and negative −) glycemic excursions (MAGE+/−), which summarizes glycemic variability by identifying glucose peaks and troughs whose amplitudes lie >1 SD outside of the mean (24); lability index (LI), which is a score based on the change in glucose levels over time (25); J-index, which is calculated using mean glucose levels and their SD (26); average daily risk ratio (ADRR), which is calculated by transforming each glucose value and then attributing risk to the transformed point so that it is possible to generate the risk attributed to low glucose (RLBG) and high glucose (RHBG) (27); glycemic risk assessment in diabetes equation (GRADE), which summarizes the degree of risk associated with variability in glucose profile (a score of <5 indicates well-controlled glucose profiles in the nondiabetic range and a score of >5 indicates periods of clinically significant hypo or hyperglycemia [28]); and mean absolute glucose (MAG), which calculates the sum of differences between successive glucose values divided by the total time over which these values are recorded (29).

FDA

Each of the glucose measurements 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 (30). This technique generates a polynomial function that describes the curve (or "spline") used to model changes in glucose levels over time for each participant, with splines required to pass through

measured glucose values at discrete time points (called "knots") during each 24-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 120-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" (FDA) (30).

Multivariable Statistical Analysis

Multivariable regression analysis was used to establish the relationship between maternal glucose levels and LGA for each of the summary statistical indices and for the FDA-generated glucose function, after adjusting for potential confounders. A directed acyclic graph (DAG) (31; see Supplementary Data) established that it was necessary to adjust for two covariates as potential confounders (type of diabetes and study center), the latter to address the potential impact of differences in the conduct of each of the original trials (particularly different sensor types, different numbers of observations per participant, and different intensities of assessment). None of the remaining covariates (age at onset of diabetes, maternal BMI, and insulin regimen) required adjustment because all fell on the causal pathway between type of diabetes and LGA. Separate regression models were fitted for data from measurement episodes within each trimester

of pregnancy to explore trimester-specific relationships between glucose levels and LGA. All statistical analyses were conducted in R (32) and Stata (33).

Ethics

All participants provided written informed consent. Ethical approval was granted by the Suffolk and Norfolk Local Research Ethics Committee and the Danish National Committee on Biomedical Research Ethics.

RESULTS

Table 1 shows the number of women and the measurements made from the original studies. CGM data were available for 132 women. Of these, 15 (11%) were not included because their CGM monitors had not generated measurements for at least one full 24-h period (n = 10), their pregnancy had resulted in twins (n = 2), or the infant's birth weight had not been recorded (n = 3). After excluding these participants, data from 117 singleton pregnancies, comprising 1.68 million glucose measurements conducted over 759 separate measurement episodes, were available for the analyses that follow. Of these 117 women, 95 (81%) had measurement episodes in trimester 1, 96 (82%) in trimester 2, and 80 (68%) in trimester 3; 89 (76%) had type 1 diabetes and 28 (24%) had type 2 diabetes; and 54 (46%) delivered an infant with LGA and 63 (54%) delivered infants who did not have LGA. Mean HbA$_{1c}$ levels (45 mmol/mol) during pregnancy indicated that these diabetic pregnancies were clinically well controlled, and there was no significant difference in mean HbA$_{1c}$ levels among mothers with LGA infants (46 mmol/mol [95% CI 44–48]) and

Table 1—Number of women available in the analysis and number of measurements in the study

	England	Denmark	Total
Number of women in analysis			
Eligible	61	71	132
Excluded	12	3	15
Included	49	68	117
Type 1 diabetes	35	54	89
Type 2 diabetes	14	14	28
Trimester 1	31	64	95
Trimester 2	44	52	96
Trimester 3	30	50	80
LGA infant	23/49 (46.9%)	31/68 (45.6%)	54/117 (46.1%)
Number of measurements	256,640	1,423,706	1,680,346
Number of measurement episodes	171	588	759

those without LGA infants (44 mmol/mol [42–46]; *P* = 0.794).

Summary Statistical Analysis

The summary statistical indices of CGM data recorded in each trimester, calculated separately for women who delivered LGA versus non-LGA infants after adjustment for confounders (type of diabetes and study), are presented in Table 2. There were statistically significant differences in the values of all but six of these indices (proportion of time below target, area under the curve <3.5 and <2.8 mmol/L, ADRR RLBG and RHBG, and MAGE−) among women with/without LGA infants. However, the indices displaying significant differences varied from one trimester to the next, as did the magnitude and direction of the differences observed. In trimester 1, LGA was associated with a significantly lower mean glucose, a lower SD of mean glucose, a lower LI, a lower J-index, and a lower MAGE+. In contrast, in trimester 2, a higher mean glucose, a higher percentage of time spent above target (and less time within target), a greater area under the curve for both >7.8 and >6.7 mmol/L, a higher M-value, a higher GRADE, and a higher MAG were all significantly associated with LGA. In trimester 3, LGA was associated with a significantly higher mean glucose and a significantly higher LI.

FDA

Figure 1 summarizes the differences in glucose levels observed throughout the 24-h day in women with LGA infants (as compared with women who did not have LGA infants) after applying FDA to CGM data from each trimester, and after adjustment for confounders (type of diabetes and study center). In each trimester, mothers who delivered LGA infants displayed significantly different glucose levels than those displayed by mothers who did not deliver LGA infants. However, the timing, duration, magnitude, and direction of these differences varied from one trimester to the next. In trimester 1, mothers who delivered LGA infants had significantly lower glucose levels from 0855 to 1105 h and from 1915 to 2135 h. In trimester 2, mothers who delivered LGA infants had glucose levels that were higher throughout both day and night and were significantly so for much of the afternoon (from 1125 to 1710 h) and

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

	Trimester 1			Trimester 2			Trimester 3		
	LGA	No LGA	Student t test[1]	LGA	No LGA	Student t test[1]	LGA	No LGA	Student t test[1]
	Mean (SD)	Mean (SD)	t^2, P	Mean (SD)	Mean (SD)	t^3, P	Mean (SD)	Mean (SD)	t^4, P
Mean glucose (mmol/L)	**7.0 (1.8)**	**7.1 (2.1)**	**16.21, <0.01**	**7.0 (1.8)**	**6.7 (1.8)**	**27.43, <0.001**	**6.5 (1.6)**	**6.4 (1.7)**	**10.61, <0.01**
Proportion of time									
In target[5]	0.63 (0.1)	0.64 (0.2)	0.75, 0.46	**0.63 (0.1)**	**0.71 (0.2)**	**3.17, <0.01**	0.69 (0.1)	0.73 (0.1)	−1.15, 0.25
Below target[5]	0.04 (0.0)	0.05 (0.0)	0.80, 0.43	0.06 (0.1)	0.05 (0.1)	0.12, 0.91	0.07 (0.1)	0.06 (0.1)	0.18, 0.86
Above target[5]	0.33 (0.1)	0.32 (0.2)	0.41, 0.68	**0.33 (0.1)**	**0.25 (0.2)**	**3.13, <0.01**	0.25 (0.1)	0.22 (0.1)	0.80, 0.43
Area under the curve (mmol/L per 5 min)									
>7.8 mmol/L	21,298 (14,599)	22,288 (16,761)	1.04, 0.30	**25,204 (19,303)**	**20,382 (16,360)**	**2.34, 0.02**	16,765 (11,822)	14,770 (12,174)	1.26, 0.21
>6.7 mmol/L	27,038 (16,348)	27,980 (17,430)	0.90, 0.37	**32,085 (20,748)**	**26,122 (17,347)**	**2.56, 0.01**	23,321 (14,017)	20,613 (18,136)	1.47, 0.14
<3.5 mmol/L	21,513 (8,127)	22,025 (8,728)	0.52, 0.60	23,810 (8,151)	23,527 (7,768)	0.29, 0.77	21,848 (7,727)	22,525 (8,539)	−0.15, 0.88
<2.8 mmol/L	17,346 (6,553)	17,735 (7,052)	0.50, 0.62	19,174 (6,541)	18,957 (6,270)	0.09, 0.93	17,623 (6,222)	18,179 (6,907)	−0.15, 0.88
SD (mmol/L)	**2.4 (0.7)**	**2.6 (1.0)**	**2.84, <0.01**	2.4 (0.8)	2.4 (0.9)	0.71, 0.48	2.2 (0.6)	2.1 (0.6)	1.00, 0.32
M-value	2,193.5 (401.4)	2,257.2 (384.8)	1.72, 0.09	**2,246.7 (348.9)**	**2,114.7 (352.5)**	**2.83, <0.01**	2,094.1 (276.2)	2,013.2 (375.5)	1.28, 0.23
LI	**1.4 (0.7)**	**1.9 (1.7)**	**3.16, <0.01**	1.5 (1.0)	1.4 (1.0)	1.26, 0.21	**1.3 (1.1)**	**1.0 (0.6)**	**2.88, <0.01**
J-index	**29.2 (8.5)**	**32.4 (15.2)**	**2.65, <0.01**	29.9 (11.4)	27.7 (11.6)	1.88, 0.06	25.0 (7.5)	23.8 (9.0)	0.94, 0.35
ADRR RLBG	1.6 (0.4)	1.5 (0.3)	−0.39, 0.70	1.6 (0.4)	1.6 (0.3)	0.34, 0.73	1.6 (0.3)	1.6 (0.3)	0.80, 0.43
ADRR RHBG	1.6 (0.4)	1.7 (0.5)	1.95, 0.05	1.6 (0.4)	1.5 (0.5)	0.65, 0.52	1.5 (0.4)	1.4 (0.4)	1.21, 0.23
MAGE+	**3.5 (1.4)**	**4.3 (2.7)**	**2.47, 0.02**	3.6 (1.6)	3.4 (1.7)	0.25, 0.81	3.3 (1.4)	2.9 (1.1)	1.14, 0.26
MAGE−	3.9 (1.9)	3.5 (1.7)	0.28, 0.78	3.5 (1.5)	3.9 (2.6)	−1.69, 0.09	3.7 (2.0)	3.0 (1.1)	1.86, 0.07
GRADE	3.9 (2.1)	3.9 (2.8)	0.59, 0.56	**3.8 (2.3)**	**3.3 (2.4)**	**2.78, <0.01**	2.9 (1.4)	2.8 (1.4)	0.58, 0.56
MAG	2.4 (0.7)	3.5 (6.0)	2.02, 0.05	**2.5 (0.8)**	**2.4 (0.9)**	**3.16, <0.01**	2.2 (0.8)	2.1 (0.7)	1.91, 0.06

[1]Comparing the difference in means to zero using a Student t test reporting the *t* value, and *P* value (boldface text indicates *P* < 0.05). Model adjusted for study and type of diabetes. [2]209 degrees of freedom. [3]297 degrees of freedom. [4]241 degrees of freedom. [5]3.5–7.8 mmol/L.

Trimester 1 Trimester 2 Trimester 3
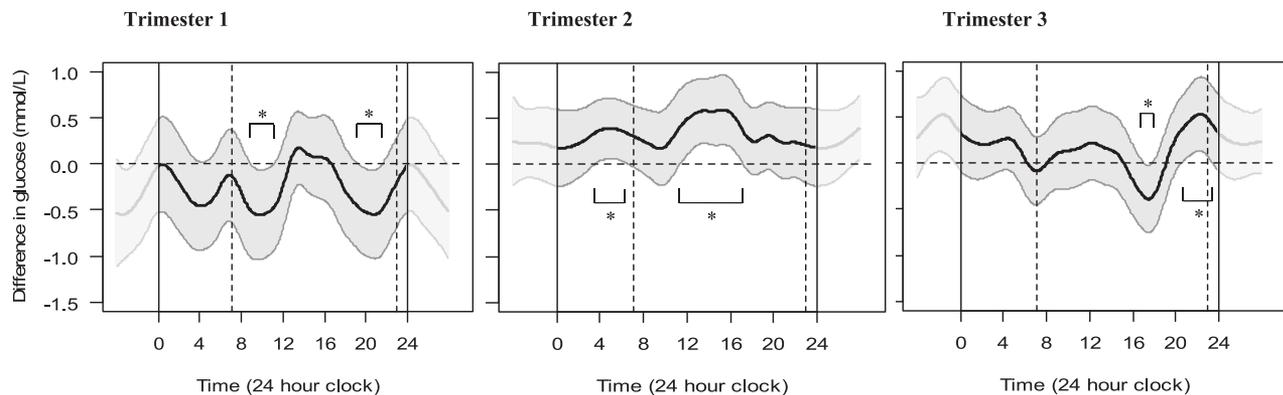
Figure 1—Difference in glucose levels between non-LGA (represented by the horizontal zero level) and LGA (dark line) with 95% pointwise CIs (gray section) (significant differences, using 95% CIs, are highlighted by *) stratified by trimester from the regression model (adjusted for study and type of diabetes). Dashed vertical lines represent 0700 h and 2300 h.

the early hours of the morning (from 0330 to 0635 h). In trimester 3, glucose levels were again higher throughout much of the day and night (and significantly so from 2035 to 2325 h), but there was also a short period in the late afternoon from 1705 to 1745 h where glucose levels were significantly lower among women who delivered LGA infants.

CONCLUSIONS

Using comprehensive standard summary statistical analyses of CGM data, this is the first study of well-controlled diabetic pregnancies to demonstrate that *1*) lower, and less variable, glucose levels in the first trimester of pregnancy are significantly associated with LGA; *2*) higher, and more variable, glucose levels in both the second and third trimester are associated with LGA; and *3*) FDA can be applied to CGM data to expose the temporal glucose profiles underlying these associations and the key contribution that relatively short-term glucose excursions during the 24-h period play therein. These temporal profiles indicate that the lower average glucose levels associated with LGA in the first trimester (Table 2) are driven by distinct dips in glucose levels midmorning and midevening (Fig. 1), whereas the higher average glucose levels associated with LGA in the second and third trimester (Table 2) are driven by significantly higher glucose levels that occur during the early hours of the morning and afternoon in the second trimester and during the late evening in the third trimester (Fig. 1). The magnitude of the transient excursions detected by FDA of CGM data

are also substantively larger (in mmol/L) than the differences in summary statistical indices of average glucose levels and glucose variability, suggesting that FDA of CGM data might offer more sensitive information for use in the clinical management of glucose control in diabetic pregnancy.

Poor glycemic control assessed by HbA_{1c} both before and during pregnancy has long been associated with accelerated fetal growth, particularly when HbA_{1c} is elevated during the third trimester (4,16,34–36). However, even when mothers and their clinicians achieve tight glycemic targets with near-normal HbA_{1c} levels, LGA continues to be a considerable problem (4,37). Our study confirms that a substantial proportion of diabetic pregnancies (in this instance >46%) result in the delivery of LGA infants, even when these pregnancies achieve reasonable control based on mean HbA_{1c} values. Given that HbA_{1c} measurements provide a retrospective measure of averaged glucose levels, they are less likely to be able to detect shorter-term variation in glucose levels that might be relevant in the development of LGA.

It is interesting that relatively lower glucose profiles during the first trimester are associated with subsequent LGA, given that clinical practice has been based on the understanding that tight glucose control in the first trimester is beneficial and does not have any adverse fetal repercussions. We postulate that the lower glucose we observe during the first trimester allows for the

development of a healthier fetoplacental unit that subsequently allows more efficient transfer of nutrients to the fetus later in pregnancy, enhancing the prospect of LGA. This is supported by work showing that fetal growth is determined in the first trimester (34) and that higher HbA_{1c} in the first trimester is associated with lower birth weight possibly due to impairment of trophoblast implantation (38).

Our data supports findings from previous studies suggesting that relatively higher glucose during the second trimester contributes to LGA (37). Our study adds to this however, by showing that the time of day most significantly associated with higher glucose is throughout the afternoon. A further period of concern is in the early hours of the morning. This may reflect a tendency for the pregnant woman and her clinical team to relax slightly after the woman gets past the initial 12 weeks knowing organogenesis is now complete. It may also represent a gradual increase in insulin resistance and a failure to keep on top of this with increasing insulin doses.

The significant difference in glucose profile in the third trimester focuses our attention on the contribution that a relatively lower glucose late afternoon, followed by a higher glucose during the evening and first part of the night, has on the association between glucose levels and LGA. Based on previous work, we hypothesize that this reflects changes in insulin responsiveness at this stage in pregnancy (39). Whereas there are no changes in glucose bioavailability or postprandial glucose

appearance between early and late gestation in type 1 diabetic pregnancy, there are significant delays in postprandial glucose disposal during late gestation, possibly due to a combination of increased peripheral insulin resistance, and a slower achievement of a maximal postprandial insulin concentration, facilitating more prolonged postprandial hyperglycemia in late pregnancy (39). Getting women to bolus their insulin up to 40 min before their evening meal may help avoid this phenomenon. An alternative would be to advise women to replace rapidly absorbed carbohydrate-rich meals for more slowly absorbed unrefined carbohydrates or to consider premeal snack primers (40) or postprandial physical activity to enhance peripheral glucose uptake.

CGM offers a potential source of data required to improve the detection and management of glucose levels in diabetic pregnancy. 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). However, one hitherto unresolved challenge has been how the detailed and complex data that CGM provides might best be interpreted. A recent call to standardize the reporting of CGM data recorded during pregnancy (17) proposed using a number of summary statistical indices. This was supported by previous research on nondiabetic obese and normal weight pregnancies (41), which found that higher average glucose levels during the third trimester were associated with neonatal adiposity, suggesting that elevated glucose levels in women exhibiting normal glucose tolerance might contribute to excess fat accumulation by the fetus. Research on 29 pregnant women with type 1 diabetes using statistical summary indices of CGM data (37) found an association between higher average daily glucose levels in each trimester and babies diagnosed as extremely LGA detected by ultrasound scan before 30 weeks gestation. However, the significant association between HbA_{1c} and birth weight in that study (37) suggests that these diabetic

pregnancies could be detected without detailed analysis of CGM.

By identifying, for the very first time, distinct temporal patterns of glucose across the 24-h day that were associated with LGA, our analyses demonstrate how FDA of CGM data might enable us to more precisely identify the specific time points at which differences in average glucose and/or glucose variability might contribute to excessive fetal growth within each trimester. This information is hidden within conventional clinical interpretations of CGM data and is not evident from any of the summary statistical indices we applied. The temporal patterns revealed by FDA tell us that short-term differences in glucose levels underlie the significant differences in summary statistical indices of average glucose levels and glucose variability across each trimester. As such, FDA of CGM data allows us to better understand where, when, and how we might better invest our efforts to optimize glucose control in diabetic pregnancy to reduce LGA and improve pregnancy outcomes.

Limitations of the Study

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. However, frequent calibration of the CGM using SMBG levels helps partly to resolve this issue. It is worth noting that we have not corrected for multiple testing and therefore there is the possibility of a type 1 statistical error in the analyses we present. There are also a number of limitations in relation to the sample of participants. The women in the study were predominantly of white European ethnicity, which may limit applicability to women from other cultures and backgrounds. The results do not include any women with gestational diabetes, and again care needs to be taken with regard to its applicability in relating to LGA in this context. All the women had conventionally good glycemic control, judged by capillary blood glucose targets and HbA_{1c}. This means that our findings cannot be generalized to women with known poor glycemic control. Further

work in this area is recommended as confidence in the observed associations would be strengthened by validation in an independent cohort.

References

1. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am 2007;34:173–199, vii
2. Feig DS, Palda VA. Type 2 diabetes in pregnancy: a growing concern. Lancet 2002;359: 1690–1692
3. Confidential Enquiry into Maternal and Child Health. *Pregnancy in Women with Type 1 and Type 2 Diabetes in 2002–2003, England, Wales and Northern Ireland*. London, CEMACH, 2005
4. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in type I diabetic pregnancy; results of a nationwide study in the Netherlands. Diabetologia 2002;45:1484–1489

5. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004;27:2819–2823

6. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177

7. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diabetes Care 2009;32:2005–2009

8. Persson M, Pasupathy D, Hanson U, Norman M. Birth size distribution in 3,705 infants born to mothers with type 1 diabetes: a population-based study. Diabetes Care 2011;34:1145–1149

9. Deierlein AL, Siega-Riz AM, Chantala K, Herring AH. The association between maternal glucose concentration and child BMI at age 3 years. Diabetes Care 2011;34:480–484

10. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007; 30:2287–2292

11. Manderson JG, Mullan B, Patterson CC, Hadden DR, Traub AI, McCance DR. Cardiovascular and metabolic abnormalities in the offspring of diabetic pregnancy. Diabetologia 2002;45:991–996

12. Rijpert M, Evers IM, de Vroede MA, de Valk HW, Heijnen CJ, Visser GH. Risk factors for childhood overweight in offspring of type 1 diabetic women with adequate glycemic control during pregnancy: nationwide follow-up study in the Netherlands. Diabetes Care 2009;32: 2099–2104

13. Sparano S, Ahrens W, De Henauw S, et al. Being macrosomic at birth is an independent predictor of overweight in children: results from the IDEFICS study. Matern Child Health J 2013;17:1373–1381

14. 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

15. Walsh JM, McAuliffe FM. Prediction and prevention of the macrosomic fetus. Eur J Obstet Gynecol Reprod Biol 2012;162:125–130

16. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008;337:a1680

17. 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

18. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care 2013;36:1877–1883

19. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med 1998;17:407–429

20. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843–848

21. NICE. Diabetes in Pregnancy. Management of Diabetes and Its Complications From Preconception to the Postnatal Period. NICE Clinical Guidelines no 63. London, RCOG Press, 2008

22. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. Diabetes Technol Ther 2009;11:551–565

23. Schlichtkrull J, Munck O, Jersild M. The M-valve, an index of blood-sugar control in diabetics. Acta Med Scand 1965;177:95–102

24. Wentholt IM, Kulik W, Michels RP, Hoekstra JB, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. Diabetologia 2008;51:183–190

25. Ryan EA, Shandro T, Green K, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes 2004;53:955–962

26. Wójcicki JM. "J"-index. A new proposition of the assessment of current glucose control in diabetic patients. Horm Metab Res 1995;27:41–42

27. Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care 2006;29:2433–2438

28. Hill NR, Hindmarsh PC, Stevens RJ, Stratton IM, Levy JC, Matthews DR. A method for assessing quality of control from glucose profiles. Diabet Med 2007;24:753–758

29. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. Crit Care Med 2010;38:838–842

30. Ramsay JO, Hooker G, Graves S. Functional Data Analysis with R and MATLAB. Dordrecht, New York, Springer, 2009

31. Law GR, Green R, Ellison GTH. Confounding and causal path diagrams. In Modern Methods for Epidemiology. Tu YK, Greenwood D, Eds. London, Springer, 2012

32. Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing, 2008

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

34. Bell R, Glinianaia SV, Tennant PW, Bilous RW, Rankin J. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. Diabetologia. 8 February 2012 [Epub ahead of print]

35. Murphy HR, Steel SA, Roland JM, et al.; East Anglia Study Group for Improving Pregnancy Outcomes in Women with Diabetes (EASIPOD). Obstetric and perinatal outcomes in pregnancies complicated by type 1 and type 2 diabetes: influences of glycaemic control, obesity and social disadvantage. Diabet Med 2011;28:1060–1067

36. Nielsen GL, Dethlefsen C, Moller M, Sorensen HT. Maternal glycated haemoglobin, pre-gestational weight, pregnancy weight gain and risk of large-for-gestational-age babies: a Danish cohort study of 209 singleton type 1 diabetic pregnancies. Diabet Med 2007;24:384–387

37. Kerssen A, de Valk HW, Visser GH. Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. Diabetes Care 2007;30:1069–1074

38. Bukowski R, Smith GC, Malone FD, et al.; FASTER Research Consortium. Fetal growth in early pregnancy and risk of delivering low birth weight infant: prospective cohort study. BMJ 2007;334:836

39. Murphy HR, Elleri D, Allen JM, et al. Pathophysiology of postprandial hyperglycaemia in women with type 1 diabetes during pregnancy. Diabetologia 2012;55:282–293

40. Chen MJ, Jovanovic A, Taylor R. Utilizing the second-meal effect in type 2 diabetes: practical use of a soya-yogurt snack. Diabetes Care 2010; 33:2552–2554

41. 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