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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Abstract (249 words, 250 max)

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 infants (LGA) born to women with diabetes.

Research design and methods - Functional data analysis 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. 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 UK and Denmark. LGA was defined as birth weight ≥90th percentile adjusted for sex and gestational age.

Results - 54/117 (46%) women developed LGA. LGA was associated with lower mean glucose (7.0 vs. 7.1mmol/l; p<0.01) in Trimester 1; with higher mean glucose in Trimester 2 (7.0 vs. 6.7mmol/l; p<0.001) and Trimester 3 (6.5 vs. 6.4mmol/l; p<0.01). Functional data analysis showed that glucose was significantly lower mid-morning (09h00-11h00) and early evening (19h00-21h30) in Trimester 1; significantly higher early morning (03h30-06h30) and throughout the afternoon (11h30-17h00) in Trimester 2; and significantly higher during the evening (20h30-23h30) in Trimester 3 in women whose infants were LGA.

Conclusions - Functional data analysis 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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Keywords

Diabetes, pregnancy, macrosomia, glucose, Continuous Glucose Monitoring, functional data analysis, circadian, diurnal

Globally, diabetes affects up to 12% of all pregnancies (1) and the proportion of pregnancies affected is increasing (2). Among women with pre-gestational (Type 1 or Type 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 (labour complications, perineal tearing, instrumental delivery and caesarean section) and perinatal (shoulder dystocia, respiratory distress, neonatal hypoglycaemia 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 hyperglycaemia 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 HbA1c 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 HbA1c measurements fail to detect 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 analyse 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 present 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 multi-centre study drew on data from two studies: one based in England (East Anglia); the second in Denmark (Copenhagen) (16; 18). Both studies recruited pregnant women with pre-gestational Type 1 or Type 2 diabetes to prospective, randomised controlled trials that explored the clinical impact of continuous glucose monitoring 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 2003-2006. In Denmark, pregnant participants, aged 19-43 years, were recruited from one diabetes antenatal clinic between 2009-2011. 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, 4-6 of which included additional study-related assessments. In Denmark, antenatal clinic visits occurred every 2 weeks, with 5 study visits undertaken at 8, 12, 21, 27 and 33 weeks gestation. Both studies used comparable glucose targets; in England <5.5mmol/L before meals, and <7.8mmol/L at 60 minutes and <6.7mmol/L at 120 minutes post-meals; in Denmark: 4.0-6.0 mmol/L before meals, 4.0-8.0 mmol/l at 90 minutes post-meal, and 6.0-8.0 mmol/L before bed.

Antenatal records provided data on: maternal BMI, HbA1c 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.

Continuous glucose monitoring (CGM)

Continuous glucose monitors were used to record electrochemically measured subcutaneous interstitial glucose concentrations every five minutes, generating 288 measurements per day. Both studies used Medtronic CGM systems (Medtronic-MiniMed, Northridge, USA), 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 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 was 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: 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 participants' exposure to high, low and normal glucose levels over time) for all glucose measurements that exceeded thresholds of 7.8 mmol/L or 6.7 mmol/L, or fell below thresholds of 3.5 mmol/L or 2.8 mmol/L (17; 21).

Measures of glycaemic variability were also calculated (22), including: standard deviation (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, then divided by the total number of glucose values to produce a mean; Mean Amplitude of (positive: +; and negative: -) Glycemic Excursions (MAGE +/-), which summarises glycemic variability by identifying glucose peaks and troughs whose amplitude lie >1SD 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 summarises the degree of risk associated with variability in glucose profile: a score of <5 indicates well controlled glucose profiles in the non-diabetic range; 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).

Functional Data Analysis

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 five minutes 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 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 120 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'.(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 appendix) established that it was necessary to adjust for two covariates as potential confounders (type of diabetes; and study centre), 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 gave 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

CGM data were available for 132 women from the original studies (see Table 1). Of these, 15 (11%) were not included because: their CGM monitors had not generated measurements for at least one full 24-hour 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, whilst 63 (54%) delivered infants who did not have LGA. Mean HbA1c levels (45mmol/mol) during pregnancy indicated that these diabetic pregnancies were clinically well-controlled, and there was no significant difference in mean HbA1c levels amongst mothers with LGA infants (46mmol/mol; 95% confidence interval [CI] 44-48mmol/mol) and those without LGA infants(44mmol/mol; 95%CI 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 vs. 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 mmol/l and <2.8 mmol/l; ADDR RLBG and RHBG; and MAGE -) amongst 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 standard deviation of mean glucose; a lower lability index; 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 >7.8mmol/l 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 lability index.

Functional Data Analysis

Figure 1 summarises the differences in glucose levels 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 from each trimester, and after adjustment for confounders (type of diabetes and study centre). In each trimester, mothers who delivered LGA infants displayed significantly different glucose levels to 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 08h55-11h05 and from 19h15-21h35. 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 11h25-17h10) and the early hours of the morning (from 03h30-06h35). In trimester 3, glucose levels were again higher throughout much of the day and night (and significantly so from 20h35-23h25), but there was also a short period in the late afternoon from 17h05-17h45 where glucose levels were significantly lower amongst 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) functional data analysis can be applied to CGM data to expose the temporal glucose profiles underlying for these associations and the key contribution that relatively short-term glucose excursions during the 24 hour period play therein. These temporal profiles indicate that the lower average glucose levels associated with LGA in the first trimester (see Table 2) are driven by distinct dips in glucose levels mid-morning and mid-evening (see Figure1), whereas the higher average glucose levels associated with LGA in the second and third trimester (see 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 (see Figure 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 glycaemic control assessed by HbA1c both before and during pregnancy has long been associated with accelerated fetal growth, particularly when HbA1c is elevated during the third trimester (4; 16; 34-36). However, even when mothers and their clinicians achieve tight glycaemic targets with near normal HbA1c levels, LGAcontinues 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

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achieve reasonable control based on mean HbA1c values. Given that HbA1c 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 HbA1c 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 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 hypothesise that this reflects changes in insulin

responsiveness at this stage in pregnancy (39). Whilst there are no changes in glucose

bioavailability or postprandial glucose appearance between early and late gestation in T1DM

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 minutes 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 pre-meal 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 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). However, one hitherto unresolved challenge has been how the

detailed and complex data CGM provides might best be interpreted. A recent call to

standardise the reporting of CGM data recorded during pregnancy (17) proposed using a

number of summary statistical indices. This was supported by previous research on non-

diabetic 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 HbA1c and birthweight 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-hour 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 optimise glucose control in diabetic pregnancy to reduce LGA and improve pregnancy outcomes.

Limitations of the study

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. However, frequent calibration of the CGM using SMBG levels helps partly to resolve this issue. It is worth noting that we haven't 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 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 glycaemic control, judged by capillary blood glucose targets and HbA1c. This means that our findings cannot be generalised to women with known poor glycaemic control. Further work in this area is recommended as confidence in the observed associations would be strengthened by validation in an independent cohort..

Ethical approval: Suffolk and Norfolk local research ethics committee and the Danish National Committee on Biomedical Research Ethics.

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

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 (46.1%)
Number of measurements	256640	1423706	1680346
Number of measurement episodes	171	588	759

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

SD = standard deviation; ADRR = Average Daily Risk Ratio; RLBG = Risk of Low Blood Glucose; RHBG = Risk of High Blood Glucose; MAGE = Mean Amplitude of Glycemic Excursions; GRADE = Glycemic Risk Assessment in Diabetes Equation; MAG = Mean Absolute Glucose

	Trimester 1			Trimester 2			Trimester 3		
	LGA Mean (SD)	No LGA Mean (SD)	t-test [1] t[2], p	LGA Mean (SD)	No LGA Mean (SD)	t-test t[3], p	LGA Mean (SD)	No LGA Mean (SD)	t-test 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 minutes)									
>7.8 mmol/l	21298 (14599)	22288 (16761)	1.04, 0.30	**25204 (19303)**	**20382 (16360)**	**2.34, 0.02**	16765 (11822)	14770(12174)	1.26, 0.21
>6.7 mmol/l	27038 (16348)	27980 (17430)	0.90, 0.37	**32085 (20748)**	**26122 (17347)**	**2.56, 0.01**	23321 (14017)	20613(18136)	1.47, 0.14
<3.5 mmol/l	21513 (8127)	22025 (8728)	0.52, 0.60	23810 (8151)	23527 (7768)	0.29, 0.77	21848 (7727)	22525 (8539)	-0.15, 0.88
<2.8 mmol/l	17346 (6553)	17735 (7052)	0.50, 0.62	19174 (6541)	18957 (6270)	0.09, 0.93	17623 (6222)	18179 (6907)	-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	2193.5 (401.4)	2257.2 (384.8)	1.72, 0.09	**2246.7 (348.9)**	**2114.7 (352.5)**	**2.83, <0.01**	2094.1 (276.2)	2013.2(375.5)	1.28, 0.23
Lability Index	**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 t test reporting the t value , and p value (bold for 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

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Figure legend

Figure 1: Difference in glucose levels between non-LGA (represented by the horizontal zero level) and LGA (dark line) with 95% pointwise confidence intervals [1] (grey section) stratified by trimester from the regression model [2]. Dashed vertical lines at 7am and 11pm.