Higher mean amplitude of glycaemic excursion in the second trimester of pregnancy is associated with the subsequent development of gestational diabetes mellitus: an observational study

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Abstract

Objective: To examine glycaemic variability (GV) and glycaemic control (GC) parameters in early pregnancy with subsequent development of gestational diabetes mellitus (GDM). Design: Longitudinal observational study. Setting: Pregnant women from KK Women and Children's Hospital in Singapore Participants: 51 study participants in the first trimester (9-13 weeks' gestational), and 44 participants (18-23 weeks' gestation) in the second trimester of pregnancy. Methods: Independent t-tests were used to examine the differences in the parameters between participants who developed GDM and those who did not. Main outcome measure: GDM was determined at 24-30 weeks' gestation using oral glucose tolerance test (OGTT). GV parameters examined were, mean amplitude of glycaemic excursion (MAGE), standard deviation of blood glucose (SDBG) and mean of daily continuous 24 h blood glucose (MBG) and coefficient of variation (CV). GC parameters measured were, J-Index and % time spent in glucose target ranges. Results: In the second trimester of pregnancy, mean amplitude of glycaemic excursions (MAGE) was significantly higher in participants who subsequently developed GDM, compared to those who did not (mean (SD): 3.18(0.68) vs 2.60(0.53), p=0.02). Other study parameters measured in the second trimester of pregnancy were not significantly different between groups. There were no significant associations between all the GV and GC parameters determined from the CGM in the first trimester with subsequent development of GDM (p>0.05). Conclusion: MAGE is an important GV parameter associated to the development of subsequent GDM in pregnant women. The findings highlight the potential value of CGM in gestational glycaemic profiling.

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Running head: MAGE and GDM development

Keywords: continuous glucose monitoring, gestational diabetes mellitus, glycaemic profiling, mean amplitude of glycaemic excursion

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ABSTRACT

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Results: In the second trimester of pregnancy, mean amplitude of glycaemic excursions (MAGE) was significantly higher in participants who subsequently developed GDM, compared to those who did not (mean (SD): 3.18(0.68) vs 2.60(0.53), p=0.02). Other study parameters measured in the second trimester of pregnancy were not significantly different between groups. There were no significant associations between all the GV and GC parameters determined from the CGM in the first trimester with subsequent development of GDM (p >0.05).

Conclusion: MAGE is an important GV parameter associated to the development of subsequent GDM in pregnant women. The findings highlight the potential value of CGM in gestational glycaemic profiling.

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Key words: Continous glucose monitoring; gestational diabetes, mean amplitude glycaemic excursion

Tweetable abstract : #CGM use and #mean glycaemic amplitude excursion associated with #gestational diabetes

INTRODUCTION

Gestational diabetes mellitus (GDM) is an abnormal glucose metabolism where blood glucose does not reach the level of overt diabetes, with onset or first recognition during pregnancy [1]. Largescale randomized controlled trials (RCTs) have shown that although, screening and treatment for GDM are associated with improved short-term outcomes [2], it failed to reduce rates of long-term outcomes such as childhood obesity [3]. This points to the need for earlier screening and detection, followed by appropriate management strategies that can help to reduce the occurrence of these adverse outcomes.

GDM is typically diagnosed using an oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. However, prospective studies have observed higher fetal adiposity [4], and growth velocity[5] as early as 20 weeks of gestational age, preceding the clinical diagnosis of GDM at 24-28 weeks of gestation. This was corroborated by Graca *et al.* [6] who reported increased amniotic fluid glucose concentrations representing maternal plasma glucose transported across the placenta as early as the second trimester in women later diagnosed with GDM. In a retrospective cohort study, "early GDM" diagnosis (at an average of 17 weeks' gestation) in pregnant women had better composite neonatal outcomes than their later-diagnosed peers (>

24 weeks) despite arguably representing a higher-risk cohort [7]. These findings indicate that the effects of hyperglycaemia of GDM mothers on the offspring are apparent at earlier timepoints (early second trimester), pointing to the potential advantages of an earlier diagnosis than the current recommended guidelines.

Glycaemic variability (GV) is defined as a degree to which blood glucose level fluctuates between high and low levels, and is emerging as an important metric used to characterize and detect subtle abnormalities in glucose metabolism under usual ambulatory conditions. With the advent of continuous glucose monitoring (CGM), it now is feasible to analyze the changes in GV indicators, and to assess glycaemic control (GC) throughout the day [8]. Furthermore, the clinical utility of the CGM to analyze GV and GC has been well demonstrated in diabetic patients (Type 1 and Type 2 diabetes) by predicting risks for diabetic complications [9, 10]. In GDM patients, GV parameters had been reported to be significantly higher in patients with GDM compared to healthy controls in several cross-sectional studies[11-14]. Contrary to those studies, there were reports of no significant differences [15] , or only borderline differences [16] in the GV parameters between the GDM and NDP group. However, these existing studies are mainly cross-sectional [12-15, 17], and conducted from the late second trimester (24 week of gestational age) onwards. To the best of our knowledge, studies assessing early indicators of GV prior to diagnosis of GDM are scarce. Moreover, available studies were primarily conducted in Western populations [11, 12, 15-17], and were not aligned to the core CGM metrics for clinical practice according to the international consensus group, which includes a CGM wear-time for a recommended 14 days and the analysis of percentage time spent in glucose target ranges [9].

To fill this gap in literature, we aimed to prospectively associate CGM-derived GV parameters and "time in ranges" in the first and second trimester of pregnancy with the subsequent development of GDM using longitudinal data from participants in the Integrating the Use of Calibration-Free Continuous Monitoring for Pregnancy Glucose Profiling (I-PROFILE) study. While some of the existing studies have only used two or three parameters to represent glycaemic variability (15, 18, 19), we chose to include a range of GV and GC parameters that are clinically relevant [18] and suitable for GDM pregnant women[10] which include: mean amplitude of glycaemic excursion (MAGE), standard deviation of blood glucose (SDBG) and mean of daily continuous 24 h blood glucose (MBG) and coefficient of variation (CV) used commonly in available studies as measures of GV[10]. J-Index and percentage of time spent-in-range (%TIR), time-above-target range (%TAR) and time-below-target range (%TBR) will be measured as GC parameters [9, 19]. During a pregnancy in women with Type I or II Diabetes and GDM, the overall goal is to increase %TIR, while reducing %TAR, %TBR and GV[9]. In this study, we hypothesize that there will be higher MBG, SDBG, %CV, %TAR and %TBR, and lower J-Index and %TIR in the first and second trimester of pregnancy in participants who developed GDM compared to those who did not.

METHODS

The Integrating the Use of Calibration-Free Continuous Monitoring for Pregnancy Glucose Profiling (I-PROFILE) study recruited 118 pregnant Singapore citizens or permanent residents in their first trimester of pregnancy between December 2018 and April 2021. This longitudinal, observational study was conducted in KK Women's and Children's Hospital which is a major public hospital in Singapore. Inclusion criteria included women of Chinese, Malay or Indian descent, aged 21 and above with singleton pregnancies. Persons with serious skin conditions (e.g., eczema) that might interfere with the compliance to the study, or those with pre-existing chronic diseases (e.g., kidney disease, Type 1 or Type 2 diabetes) were excluded from participation. The study was approved by the Sing Health Centralised Institutional Review Board (reference number 2018/2128). All participants gave written informed consent in accordance with the Declaration of Helsinki.

In the first trimester and second trimester, there were 51 and 44 pregnant women with complete continuous glucose monitoring (CGM) data and gestational diabetes mellitus (GDM) outcomes, respectively (Figure 1). A subset of n=43 with complete CGM data at both time points were used for sensitivity analyses.

Continuous glucose monitoring (CGM)

At the recruitment visit in the first trimester of pregnancy (9-13 weeks gestational age), participants will

be first randomized to have either a blinded CGM sensor (sensor without a reader) (FreeStyle® LibreTM, Abbott Diabetes Care, Alameda, CA) or a non-blinded sensor (sensor with a reader) (FreeStyle Libre Pro ®, Abbott Diabetes Care, Alameda, CA) inserted on the back of either right or left upper arm on day 0, and worn up to 14 days. Glucose levels will be recorded from the interstitial fluid every 15 minutes, CGM data were downloaded from the reader for the blinded sensors, or using a software, LibreView for the non-blinded sensor users. Participants were inserted with a new sensor at the second trimester (18-23 weeks of gestational age) clinic visit. Only data from the non-blinded sensor with 70% of data captured using the sensor was used for analysis [20]. The following variables were calculated from CGM readings for each participant: Mean amplitude of glycaemic excursion (MAGE), Standard deviation of blood glucose (SDBG), Mean of daily continuous 24 h blood glucose (MBG), % Coefficient of variation (CV), % of time spent in glucose target ranges and the J-Index. The % of time in target ranges were defined as: %TIR (3.5–7.8 mmol/L), %TAR (>7.8mmol/L, and %TBR (<3.5mmol/L)[9]. J-index, is a parameter of glucose control[21], while MAGE, quantifies major swings of glycaemia and excludes minor ones was considered the gold standard for assessing intra-day glycaemic variability [22] . Extracted CGM data was used to calculate MBG, SDBG, MAGE, %CV and J-Index by an automated Software EasyGV version 9.0.R2.

Ascertainment of gestational diabetes mellitus (GDM)

Participants underwent a 75-g oral glucose tolerance test (OGTT) at 24-30 weeks' gestation; fasting (FG), 1-h plasma glucose (1hPG) and 2-h plasma glucose (2hPG) concentrations were obtained using an automated biochemical analyzer (Abbott Alinity). Plasma glucose concentrations were used to classify GDM according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: if any one of the plasma glucose values was at or above the following thresholds: 5.1 mmol/L for FPG, 10.0 mmol/L 1hPG and 8.5 mmol/L for 2hPG.

Maternal data collection

Participants were followed up at the recruitment visit in the first trimester of pregnancy (9-13 weeks) and at 18-23 weeks gestation in the second trimester of pregnancy. Questionnaires were administered to collect information on demographics, socio-economic status, lifestyle, obstetric and medical history. Pre-pregnancy weight was self-reported while height at early pregnancy was measured in the prenatal care clinic at KKH using the Avamech B1000-M. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height^2 (m^2).

Statistical analysis

Univariate analyses were conducted to describe and compare the demographic factors, anthropometric measurements, medical history, OGTT readings, GV and GC parameters between group diagnosed with GDM and the group without GDM. Group differences were evaluated using Student's t -test or the Wilcoxon rank-sum test for continuous variables, and the chi-square and Fisher's exact tests were used for categorical variables. Descriptive statistics for numerical variables were presented as mean (SD), or median (interquartile range) and n (%) for categorical variables. Statistically significant results were determined at 2-sided $p < 0.05$, and p<0.01 were described as non-significant trends. Statistical analyses were performed using STATA software version 13.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Baseline characteristics of study participants

In 51 study participants, the only significant difference in characteristics between the group of pregnant mothers who were diagnosed with GDM (n=8) at a mean gestational age of 25.8 (+ 2.55) weeks, compared to those who did not (n=43), was the 1-hour OGTT glucose values (11.0 + 4.15 vs 7.27 + 1.45 mmol/L, p<0.04) (Table 1). The distribution of the type of CGM sensor (blinded or unblinded) worn, and the mean wear-time (14 days) did not significantly differ between the two groups. The characteristics of the participants who were included (n=51) and excluded (n=67) in the analyses were not significantly different (Supplementary Table S1).

CGM glycaemic profiles between study participants who developed GDM and those who did not

GV detected from the CGM of women in the first trimester of pregnancy who developed GDM and those who did not were presented in Table 2. There were no statistically significant differences in the GV parameters at the time of CGM application at an average of 10 weeks of gestational age. CGM application in the second trimester of pregnancy at an average of 20 week of gestational age was associated with higher MAGE in the group of women who developed GDM (3.18 + 0.68 vs 2.60 +0.53 mmol/L, p =0.02) compared to those who did not (Table 3). Other parameters analyzed such as MBG, SDBG, %CV, J-Index, MAGE, %TIR, %TAR and %TBR were not significantly different between the two groups. It is notable that in both the first and second trimester of pregnancy, there were consistent non-significant trends of higher MBG, SDBG and %TAR, but lower %TIR in the group who developed GDM.

In sensitivity analyses (n=43), similar associations were observed with only MAGE being higher in the GDM group compared to the non-GDM group (3.18 + 0.68 vs 2.59 + 0.54, p =0.02). In addition, there were non-significant trends observed with a higher %TAR [(median 1.57, Interquartile range (IQR), 0.5-3.82) % vs 0.36 (IQR 0.04-1.37) %, p =0.09] and a lower %TBR [(9.7(IQR1.7- 11.2) % vs 15.7 (IQR7.4-31.1) %, p=0.09] for participants who developed GDM compared to those who did not (Supplementary Table S2).

DISCUSSION

Our study which utilizes the CGM sensor data to analyze GV and GC parameters, is the first to be conducted in Singaporean pregnant women who are relatively at higher risk for GDM, compared to women of Western ethnicity [23]. In the second trimester of pregnancy, we find that MAGE was significantly higher in the group of women who subsequently developed GDM, compared to those who did not. Our findings contribute to the much-needed evidence examining the associations between GV and GC parameters early in pregnancy, and the subsequent development of GDM in pregnant women.

Only three studies [11, 13, 16] thus far have included MAGE from CGM data as a GV parameter when examining GDM as an outcome. Our findings concur with the cross-sectional study by Su *et al.*[13], which reported significantly higher levels of MAGE in pregnant women who were diagnosed with GDM at an average of 25 weeks of gestational age, compared to pregnant women who did not develop GDM, and non-pregnant healthy women with normal glucose regulation. Similarly, Dalfra *et al* . [16] reported an overall trend of slightly higher MAGE levels across the first, second and third trimester of pregnancy in women who developed GDM, compared to healthy control, although the significance was merely borderline. However, when MAGE levels were assessed independently in different trimesters of pregnancy in another study by Dalfa *et al.,* the levels of MAGE were reported to be lower, but higher in the second and third trimester respectively, in participants with GDM outcomes compared to the healthy controls [11]. Still, they only used CGM data after a short wear-time of 2 days which might not be sufficient to optimally asses glycaemic control [20], and a GDM diagnosis across a wide timepoint with an average of 21 weeks of gestational age with an SD of 6.3 weeks which might result in misclassifications[1], possibly explaining the discrepancies in study findings.

MAGE was the first diabetes-specific GV metric to be developed primarily to capture mealtime-related and intra-day glucose excursions, and has been considered a gold standard for assessing GV. It had been associated with increased insulin resistance, and early-phase insulin secretion deterioration [13], which is characteristic of the pathophysiology of GDM and Type 2 Diabetes development[24]. Furthermore, higher MAGE levels which represents greater glucose fluctuations had been associated with adverse maternal and neonatal outcomes attributed by GDM, including large for gestational age, small for gestational age, higher birth weight, neonatal hypoglycaemia [25].

The differences in MAGE levels in the group who developed GDM compared to the group who did not was only significantly different in the second trimester, but not the first. This observation can be explained by the physiological changes in the action and secretion of insulin, where serum insulin levels progressively increase from the first to the third trimester of pregnancy, signifying an increase in insulin resistance as the pregnancy advances [26]. This can then be correlated to higher glucose variability exacerbated by glycaemic

instability in the later trimesters of pregnancy as seen in a study by Dalfra *et al.* The authors of this study reported an overall increasing trend of GV parameters (MAGE, SDBG, CONGA continuous overlapping net glycaemic action, interquartile range (IQR)) from the first to the third trimester of pregnancy in both healthy pregnant women, and in pregnant women with GDM [16]. Our findings coupled with the available evidence from literature allude to inherent differences in MAGE levels in pregnant women diagnosed with GDM, compared to those without GDM which is likely to be more pronounced starting from the second trimester of pregnancy.

In our study, MBG, SDBG, CV, J-Index, %TIR, %TAR and %TBR were not significantly associated with GDM outcomes. However, across existing literature these CGM-derived parameters had not been shown to be consistently associated with GDM outcomes. Three studies reported MBG to be significantly higher in the group of women who developed GDM[13, 14, 16], one study reported significant associations only the second trimester but not the third trimester of pregnancy, [11] while another three reported null associations [12, 15, 17]. Amongst these studies, only four analyzed SDBG [11, 13, 16, 17], and only two found significant associations with GDM outcomes [13, 16], one study reported higher SDBG in the GDM group only in the third trimester, but lower SDBG in the second trimester compared to the controls[11]. So far, only one other study has analyzed CV, J-Index and time in glucose ranges (%TIR, %TBAR and %TBR) and reported null associations with GDM outcomes [17].

The strengths in our study lie in its' prospective design, which enables us to assess the temporal sequence of the GV and GC parameters measured by the CGM in the first and second trimester of pregnancy on subsequent GDM development. Unlike other studies which have explored similar associations, our study has analyzed CGM data from an average of 14 days wear-time to acquire a more accurate and meaningful interpretation of the glucose data. Furthermore, our GDM diagnosis uses the IADPSG criteria adopted by the World Health Organization, while other studies in literature have used different diagnostic criteria for GDM[12, 14, 16, 17], and thus different glucose thresholds in a two- or three-time-point antenatal OGTT for diagnosis. All in all, our findings corroborate with other studies in terms of the applicability of CGM use in detecting GV and GC parameters during pregnancy.

A few limitations were noted in this study. Firstly, our small sample size limits the generalizability of its findings, and secondly, this observational study cannot establish a causal relationship between MAGE and the increased risk for the development of GDM.

CONCLUSION

Our study has shown an association between higher MAGE and women who subsequently develop GDM. Our study demonstrated the use of the CGM sensor during pregnancy to be a promising, and applicable technology in gestational glucose profiling to determine GV and GC parameters in a convenient, and pain-free manner. Early pregnancy presents a unique opportunity for early GDM risk stratification to allow for earlier lifestyle interventions to prevent adverse maternal and child health outcomes [27]. More future studies are required on a larger scale to eventually establish a gold standard metric using CGM-derived data in terms of predicting the risk for GDM development.

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AUTHOR DISCLOSURE STATEMENT

No authors report any potential conflict of interest.

AUTHOR CONTRIBUTION

P.L.Q. contributed to the design of the study, the statistical analysis and the writing of the manuscript. N.S.R. and N.S.R. both contributed to the data collection. K.H.T. contributed to the design of the study.

K.H.T. and P.L.Q. were responsible for finalizing the manuscript. All authors contributed to and approved the final manuscript.

DETAILS OF ETHICS APPROVAL

The study was approved by the Sing Health Centralised Institutional Review Board (reference number 2018/2128).

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