Continuous glucose monitoring feedback in the subsequent development of gestational diabetes: a randomised controlled trial in pregnant women

Phaik Ling Quah[1], Lay Kok Tan[2], Ngee LEK[2], Shephali Tagore[2], Bernard, Su Min Chern[2], Seng Bin Ang[2], Ann Wright[2], Serene Thain[2], and Kok Hian Tan[1]

[1]University of Leeds Section of Obstetrics and Gynaecology
[2]KK Women's and Children's Hospital

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Abstract

Objective: To examine CGM feedback with the subsequent development of gestational diabetes (GDM), maternal glycaemic control, and glycaemic variability during pregnancy with randomisation 1:1 with one study arm receiving CGM feedback by intermittent scanning (unblinded group), versus masked feedback (blinded group). **Design:** Prospective, single-center, randomized controlled trial **Setting:** Single tertiary care hospital **Population:** Pregnant women recruited in the first trimester of pregnancy **Methods:** We assessed GDM and plasma glucose levels diagnosed by the 75-g oral glucose tolerance test (OGTT) at 24-28 weeks as a primary outcome. The secondary outcome was CGM-derived parameters of glycaemic variability across the first (9-13 weeks), second (18-23 weeks), late second and early third (24-31 weeks) and third trimester (32-33weeks). **Results:** Over 47 months, 206 pregnant women were enrolled at 9-13 weeks. There were no significant differences with GDM outcomes, fasting, 1-hour or 2-hour plasma glucose concentrations between study arms. The unblinded group had higher %time-in-range in the first (83.2% vs 78.1%; p=0.06), second [88.7% vs 80.5%; p=0.02] and third trimester (90.2% vs 79.5%; p=0.07), compared to the blinded group. Conversely, the unblinded group had lower %time-below-range in the first trimester (15.4% vs 21.2%; p=0.06), and early second trimester (8.8% vs 16.9%; p=0.05]. No significant differences were observed with the %time-above-range, mean, standard deviation, Mean Amplitude Glycaemic Excursion and % Coefficient Variation across all trimesters. **Conclusion**: CGM feedback, coupled with better glycaemic control (higher %TIR and low %TBR) indicates its' potential use in combination with appropriate patient education for promoting better glucose control during pregnancy.

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[1]Division of Obstetrics & Gynaecology, KK Women's and Children's Hospital, Singapore

[2]Department of Maternal Fetal Medicine, KK Women's and Children's Hospital, Singapore.

[3]Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Singapore.

[4] Duke-NUS Medical School, Singapore

[5] Minimally Invasive Surgery Unit, KK Women's and Children's Hospital, Singapore.

[6]Family Medicine Service/Menopause Unit, KK Women's and Children's Hospital, Singapore.

Running title: A randomised controlled trial using continuous glucose monitoring sensors in pregnant women.

Corresponding author

Quah Phaik Ling, Division of Obstetrics and Gynaecology in KK Women's and Children's Hospital (KKH), Singapore, 100 Bukit Timah Rd, Singapore 229899.

Email: quah.phaik.ling@kkh.com.sg

Telephone number: +65 97732543

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ABSTRACT

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Results: Over 47 months, 206 pregnant women were enrolled at 9-13 weeks. There were no significant differences with GDM outcomes, fasting, 1-hour or 2-hour plasma glucose concentrations between study arms. The unblinded group had higher %time-in-range in the first (83.2% vs 78.1%; p=0.06), second [88.7% vs 80.5%; p=0.02] and third trimester (90.2% vs 79.5%; p=0.07), compared to the blinded group. Conversely, the unblinded group had lower %time-below-range in the first trimester (15.4% vs 21.2%; p=0.06), and early second trimester (8.8% vs 16.9%; p=0.05]. No significant differences were observed with the %time-above-range, mean, standard deviation, Mean Amplitude Glycaemic Excursion and % Coefficient Variation across all trimesters.

Conclusion : CGM feedback, coupled with better glycaemic control (higher %TIR and low %TBR) indicates its' potential use in combination with appropriate patient education for promoting better glucose control during pregnancy.

Clinical trial

Date of registration: November 17,2021

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INTRODUCTION

The size and duration of glucose fluctuations throughout the day govern the overall daily glycaemic control. This is particularly significant during pregnancy in which physiological changes promote diabetogenesis. Furthermore maternal normoglycaemia is associated with lower risk for complications in patients with Type 1 Diabetes (T1D)[1-4] ,Type 2 Diabetes (T2D) [1, 4,5]. Pregnant women with gestational diabetes (GDM) have been shown to have greater blood glucose fluctuations with higher mean and standard deviations in glucose levels[6-8] and a greater mean amplitude of glycaemic excursion (MAGE)[6, 8] compared to pregnant women without GDM (non-diabetic pregnancies)[9].

Continuous glucose monitoring (CGM) is a way of objectively, accurately, and painlessly measuring these blood glucose variations[5, 9, 10]. Previous studies on CGM use in pregnancy were based on earlier versions of CGM sensors that required calibration[1], masked the glucose readings [2, 3]and only had a sensor-life of 3 [2, 3] to 6 days[1, 4]. In September 2016, the U.S. Food and Drug Administration (FDA) approved the Freestyle Libre Pro Glucose Monitoring System, a calibration free-continuous glucose monitoring (CF-CGM) system for blinded professional use in clinics, and in September 2017, the Freestyle Libre for unblinded personal use by patients became available. These sensors are factory calibrated and require no participant or healthcare professional involvement. Both systems have a disposable sensor which is applied to the back of a patient's arm and can be worn for up to 14 days ensuring adequate data is available for clinical evaluation [11]. With the Freestyle Libre Pro, a handheld device is used to download the blood glucose information stored in the sensor at the end of the 14-day wear, but the glucose data is not visible during the time of application. Patients using the Freestyle Libre can receive CGM feedback any time by intermittently scanning the sensor. [12].

Evidence in the form of randomized-controlled trials (RCTs) and cohort studies suggests that the control of glycaemic variability, characterized by glucose excursions and fluctuations can be better managed with CGM feedback during pregnancy [13-16]. Being able to rapidly identify the consequences on blood glucose level of factors such as diet and exercise and make behavioural changes accordingly has been found to improve maternal glycaemic control. Moreover, it has led to better obstetric and neonatal outcomes, in studies involving pregnant women with T1D[16], T2D[13] and gestational diabetes[9, 14]. The ease of interpretation the glucose readings from CGM feedback can empower, and serve as an educational tool for patients to better manage their glucose levels during pregnancy [5, 9, 15]. However all the randomised trials to date have been conducted in diabetic patients[13, 14, 16] who are already highly motivated to improve their glycaemic control and no studies have been conducted in healthy non-diabetic pregnant women.

To our knowledge, our study is the first to evaluate the benefits of CGM feedback throughout pregnancy in women without pre-existing Type I or Type II diabetes. The primary aim of this randomized controlled trial (RCT) study was to compare GDM outcomes and plasma glucose levels from the oral glucose tolerance test (OGTT) between users receiving CGM feedback and those who were not. The secondary aim was to compare maternal glycaemic control, and glycaemic variability in the first, second, late-second to early-third, and third trimesters of pregnancy between the two groups. We also explored user acceptability of both groups towards the use of their respective sensors. We hypothesize that receiving CGM feedback will result in lower OGTT glucose values, and a lower prevalence of GDM development (primary outcome) with improved glycaemic control and glycaemic variability parameters throughout pregnancy (secondary outcome).

METHODS

Study design

The Integrating the Use of Calibration-Free Continuous Monitoring for Pregnancy Glucose Profiling (I-PROFILE) study was a prospective, single-center, randomized controlled trial conducted at the Depart-

ment of Obstetrics and Gynaecology, KK Women's and Children's Hospital, a major public hospital in Singapore. 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. Protocol details are available at ClinicalTrial.gov (clinical trial reg. no. NCT05123248) and summarized below. The data that support the findings from this study are available from the corresponding author upon request. CONSORT reporting guidelines were used in the reporting of the study findings [17].

Study population and eligibility criteria

Eligible participants suitable for recruitment in this I-PROFILE study included pregnant women in their first trimester of pregnancy between December 2018 and November 2022. Participants were randomly divided into two groups of a 1:1 ratio: The unblinded group received the Freestyle Libre CGM sensor (Abbott Diabetes Care, Alameda, California, USA), and the blinded study group received the Freestyle Libre Pro CGM sensor (Abbott Diabetes Care, Alameda, California, USA). Inclusion criteria for the study included: women of Chinese, Malay or Indian descent, aged 21 and above with singleton pregnancies. Exclusion criteria included: patients with skin conditions such as, eczema which could potentially affect compliance or those with pre-existing chronic diseases including, kidney disease and pre-gestational diabetes.

Between December 2018 and November 2022, 931 patients were screened for eligibility and 712 had to be excluded because of the following reasons: 1) did not meet the study inclusion criteria (n = 225) 2) declined study participation (n = 469) 3) dropped out of the study before the randomization (n = 8) 4) had a miscarriage and was no longer eligible to participate (n = 10). Out of the n=219 participants who were randomized into the two study arms, n=206 have completed the study (Figure 1).

Trial design

Following informed consent of all eligible participants at the initial clinic visit, randomization was achieved using opaque envelopes as a method of allocation concealment. Since this was a non-blinded trial, the CGM sensor to be used was clearly visible to both the study participant and research staff. The participants were allocated to the unblinded study group (Freestyle Libre) or the blinded group (Freestyle Libre Pro). The flow of the study clinic visit schedule is shown in Figure S1. There were 4 scheduled clinic appointments for all participants, and GDM was routinely screened for between 24-28 weeks with the 75-g 3- point oral glucose tolerance test (OGTT)[18] (Figure S1).

Continuous glucose monitoring

All study participants inserted and wore a CGM sensor on the back of either their right or left upper arm, without any over-bandage for up to 14 days. Participants in the blinded group wore the sensor for 14 days without a reader. Neither the participant nor the study team members had access to the data recorded by the CGM sensor during this time. At the end of the 14-days the participant were to scan the sensor using the blinded-reader by themselves or there were assisted by a clinical research coordinator in the clinic, and the data from the reader was downloaded to a research computer. Participants in the unblinded group wore the sensor for 14 days with an open reader which provided them glucose readings each time the sensor was scanned. The participants were requested to upload their glucose readings every 8 hours, or at least three times a day where possible using the reader provided, but were allowed to scan their glucose levels as often as they wanted. After each 14-day wear- period all participants were asked to dispose of the used sensor and received a new sensor according to the study clinic visit schedule (Figure S1). Apart from the type of CGM sensors allocated, all participants were assessed in the same way.

Primary outcome: Ascertainment of glucose concentration and gestational diabetes (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.

Secondary outcome: Analyses of CGM data

Data from the CGM was extracted for use with a minimum wear-time of 7 out of 14 days (50% of data captured) at four timepoints during pregnancy: first trimester (9-13 weeks gestation), early second trimester (18—23 weeks), late-second to early-third (24-28 weeks) gestation) and third trimester (32-33 weeks of gestation). The following variables were calculated from CGM readings for each participant: Percentage time-in-range (% TIR), percentage time-above-range (% TAR), percentage time-below-range (% TBR), mean glucose, standard deviation (SD), percentage coefficient of variation (%CV) and mean amplitude of glycaemic excursion (MAGE). 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) and were used to assess glycaemic control [11]. MAGE, quantifies major swings of glycaemia and excludes minor ones was and is considered the gold standard for assessing intra-day glycaemic variability [19], along with SD and %CV. Extracted CGM data was used to calculate mean glucose, SD, %CV and MAGE, by an automated Software EasyGV version 9.0.R2.

Self-reported assessment on acceptability and satisfaction of device use

Participants completed a semi-structured questionnaire developed by our research team on patient satisfaction with the use of the CGM sensors on a 5-point Likert Scale (1=

Highly disagree, 2= Disagree, 3= Neither agree nor disagree, 4=Agree, 5= Highly agree). All participants were asked to complete the questionnaire at the fourth clinic visit at 32-33 weeks of pregnancy, except for participants who were diagnosed with GDM who completed the questionnaire at the sixth clinic visit at 6-12 weeks postpartum (Figure S1).

Maternal data collection

Participants were seen at the recruitment visit in the first trimester of pregnancy (9-13 weeks) and at 18-23 weeks gestation in the early 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 antenatal 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

This study is the first randomised controlled trial pilot and feasibility study using CGM sensors in pregnant women comparing a group with CGM feedback and a group without. The actual value of standardised effect size to be used was not known before this pilot trial. When estimating the sample size, we used a simple method by applying the rules of thumb by Teare et al. which recommended a pilot trial sample of at least 120 (60 in each study arm) if the primary outcome of the trial is binary [20].

The analyses were conducted on the intention-to-treat principle which includes all the women who participated in the randomization and completed the study (Figure 1). Categorical variables were summarised by counts and proportions; continuous variables data was summarised by means and standard deviation (SD), or by median and interquartile range (IQR) in the case of deviations from the normal distribution. The primary analysis used multivariable logistic regression to assess the associations between the two study arms (unblinded and blinded) with GDM outcomes, and multivariable linear regression to assess the associations between CGM groups and OGTT FG, 1hPG and 2hPG concentrations. Regression models were adjusted for covariates such as maternal age, ethnicity, education, family history of diabetes and pre-pregnancy BMI with the vce (robust) option without multiple imputation as the percentage of missing covariate data was very low (<2.0%).

From the total number of participants, 206, who were randomized and completed the study, 40 were excluded leaving 79 in the unblinded group and n=87 in the blinded group to be included in the final analysis examining

the primary outcomes (Figure 1). These participants would have had to wear the CGM sensors at the 4 timepoints: first trimester at 9-13 weeks, the early second trimester at 18-23 weeks, late-second to early-third 24-28 weeks and the third trimester at 32-33 weeks (Figure S1). The secondary analysis used all available data at the four different timepoints, and the cross-sectional differences in the CGM parameters (such as %TIR, %TAR, %TBR, mean glucose, SD, MAGE and %CV) between the CGM groups was assessed using linear regression at all four timepoints. The regression model was adjusted for maternal age, ethnicity, education, family history of diabetes, GDM outcomes, gestational age of CGM application and pre-pregnancy BMI with the vce (robust) option without multiple imputation as the percentage of missing covariate data was very low (<3.0%). The data from the CGM with less than 50% of data captured at all the timepoints of interest (from the first to the third trimester) was excluded from further analysis; in total, 45 from the unblinded study arm and 58 from the blinded study arm were included in the final analysis (Figure 2). A two-sided p value <0.05 is considered statistically significant, and p value <0.1 was reported as trends for both primary and secondary outcomes. All analyses were performed by using the statistical software STATA 13.1.

RESULTS

Baseline characteristics

The participants in both the unblinded and blinded study arm groups had comparable baseline characteristics as presented in Table 1. Of the total participants, approximately 60% were Chinese, 90% had at least a college education and above, and 50% had a family history of diabetes. Participants had a mean age of 31 years and a pre-pregnancy BMI of 22 kg/m^2. The mean gestational age at which the CGM sensors were worn by participants after randomization was 11 weeks, and the mean gestational age of OGTT assessment was 25 weeks (Table 1). There were no differences in baseline characteristics in the participants included and excluded from the analysis with the primary outcome of GDM (Table S1).

Primary outcomes

The differences between the GDM outcomes and OGTT plasma glucose concentration values in both study arms are shown in Table 2. There were no significant differences in the proportion of pregnant women diagnosed with GDM in the unblinded group compared to the blinded groups [21.5% vs 14.9%, p =0.37]. There were also no significant differences in the FG,1hPG and 2hPG of participants in the unblinded group, compared to the blinded group group [FG: median 4.2 IQR 4.0-4.5) vs 4.3 (4.1-4.6) mmol/L, p =0.48); 1hPG: 7.7 (6.3-9.2) vs 7.5(6.3-8.7) mmol/L,p =0.38), and 2hPG: 6.3 (5.8-7.7) vs 6.2 (5.3-7.2) mmol/L,p =0.15)]. Adjustments were made for co-variates such as maternal age, ethnicity, education, family history of diabetes and pre-pregnancy BMI.

Secondary outcomes

The CGM parameters between the unblinded and blinded groups across the three trimesters of pregnancy that represent glycaemic control (%TIR, %TAR and %TBR) are presented in Figure 2, and parameters including mean glucose and glycaemic variability (SD, MAGE and %CV) are presented in Figure S2. There were trends of higher %TIR in the first trimester [83.2% (74.1- 93.9) vs 78.1% (58.9-87.1); p=0.06], and third trimester [90.2% (77.9-95.8) vs 79.5% (65.1-90.4); p=0.07], compared to the blinded group users. Significant associations were only seen in the early second trimester of pregnancy at 8-13 weeks [88.7% (76.4-92.7) vs 80.5% (59.6-90.4), p=0.02]. Conversely, there was a trend of lower %TBR in the first trimester [15.4 (4.09-24.9) vs 21.2 (11.3-38.5); p=0.06], and the early second trimester [8.8 (5.4-20.9) vs 16.9 (6.4-34.2); p=0.05] (Figure S2 and Table S2). There were no significant differences between the unblinded and blinded groups for %TAR, mean, SD, MAGE and %CV levels (Figure S2).

Acceptability and satisfaction from CGM use

A significantly higher proportion of participants in the unblinded group agreed that it was relevant (93.3% vs 76.9%, p =0.005) and were motivated to track their daily behaviours (92.0% vs 75.6%,p =0.006), compared to participants in the blinded group (Table S3). Overall, the participants in the unblinded group had a higher user satisfaction score (4.4 + 0.7 vs 4.1 + 0.5,p =0.002) than the blinded group. However, the proportion

of CGM users having at least 70% of the CGM data captured from the total wear-time was lower in the unblinded group, compared to the blinded group (32.1% vs 70.1%, p =0.002) (Table S3). Adverse events occurred in 29.3% from those in the unblinded group, and in 36.7% from the blinded group, with the most common adverse event being skin reactions at the site of sensor application (Table S4). Amongst the users in the unblinded group, >90% reported that they would scan their sensors at 4- or 8-hour intervals, and 36% reported that they never missed a scan. Approximately 56% were not motivated to change their lifestyle behaviours and 81.3% never correlated their meal intake with use of the sensor (Table S5).

DISCUSSION

In this prospective randomized controlled trial study, pregnant women in the unblinded group did not show any significant differences in the primary outcomes of GDM development and OGTT plasma glucose concentrations. However, the unblinded group did display a trend towards better glycaemic control seen with higher time spent in target glucose range percentages (3.5-7.8 mmol/L) in the first, followed by the early second and third trimesters of pregnancy, and lower time spent below the glucose range percentages (<3.5mmol/L) in the first and early second trimesters. There were no significant differences seen in the %TAR, mean, %CV, SD and MAGE values between the two CGM groups.

To the best of our knowledge, this is the first study to compare CGM sensor users with and without CGM feedback in women without pre-existing Type 1 or Type II Diabetes, early in pregnancy before the diagnosis of GDM. Our study did not show a reduction in GDM prevalence between the unblinded group over the blinded group users. To date, there has been only one RCT reporting the beneficial effects of CGM feedback using a real-time CGM sensor, comparing it to capillary glucose monitoring and users with masked CGM feedback in pregnant women with type 1 diabetes (CONCEPTT) trial. In this study, the improved neonatal outcomes reported with the receipt of CGM feedback were attributed to reduced exposure to maternal hyperglycaemia as mothers spent more time within their target glucose range [16]. The null associations with GDM development were also reflected by the null associations in the plasma FG,1hPG, and 2hPG levels between the two study arms.

Direct comparisons to the CONCEPTT study are difficult due to differences in study design. The CONCEPTT study recruited pregnant women who were already diabetic in whom careful monitoring of glucose levels was anyway required for insulin dose adjustment. Such participants would be anticipated to be more motivated in self-management of their glucose levels through lifestyle modification. By comparison, our study participants were healthy at recruitment in early pregnancy, and before any diagnosis of GDM. In contrast to our study which provided participants with a new CGM device after an interval of 6-9 weeks, the CONCEPTT study participants had their CGM replaced every month. Participants in the CONCEPTT study were also provided a real-time CGM which provides alerts and active alarms, transmits a continuous stream of glucose data in real time, and has been shown to be more effective in promoting better glycaemic control. In contrast, our study participants received an intermittently scanned CGM sensor which requires the user to purposely scan the sensor to obtain the same information, and lacks alerts and alarms. [21] Furthermore, we have noted that out of the 79 participants in the unblinded group who remained in the study after recruitment, almost half (43%) failed to provide at least 50% of the CGM glucose data from not scanning their sensor regularly. The low compliance to have sensors scanned at least every 8 hours would mean that not all participants in this group have fully benefitted from the CGM feedback.

Our study showed that there was overall better glycaemic control throughout the pregnancy as seen from higher %TIR in the unblinded group. There was also trend of lower %TBR in the unblinded group during the first and early second trimester. Our observations on time spent in target glucose range concurred with those of the CONCEPTT study which compared glycaemic control parameters in a group receiving CGM feedback compared to those without at 34 weeks gestation [16]. In contrast to our findings, the CONCEPTT study found no significant difference in women with glucose values below the target range and a reduced percentage of women who spent time above the target glucose range [16]. These discrepancies in findings are mainly attributed to the population of non-Type I or Type II diabetic women in our study sample. GDM patients and non-GDM pregnant patients have mild hyperglycaemia, and higher incidences of hypoglycaemia

compared to patients with Type 1 or Type II Diabetes [22]. In our study, the percentages of participants who spent time above the target glucose range were low, with a median less than 1% and minimum and maximum percentages between 0-2%, as most of the women in this sample were healthy and less likely to be hyperglycaemic.

There were no differences in the mean glucose, SD, %CV and MAGE values except for higher mean concentrations in the unblinded group at the time points (9-13 weeks and 18-23 weeks. In contrast to our study, the CONCEPTT study reported significantly reduced glucose SD, lower MAGE, and non-significantly reduced glucose coefficient of variation, suggesting less glycaemic variability and better glycaemic control in the users of the unblinded real-time CGM group [16]. These findings may possibly be explained by the use of the intermittently scanned CGM in our study which has been shown to be less successful in controlling mean glucose values and %CV[23] compared to the real-time CGM. Our observations suggest participants in the unblinded group were more motivated to use the sensor for tracking their daily behaviours. However, despite this, the self-reported data showed that 44% of participants in this group did not modify their diet nor physical activity level, and 68% did not keep track of their dietary intake despite receiving CGM feedback. Future studies examining CGM feedback in pregnant patients who are healthy at the time of recruitment should be coupled with better patient education and personal guidance to achieve better glycaemic control and glycaemic variability CGM parameters [24].

Our study is the first to compare CGM with feedback and without in healthy pregnant women without Type I or II diabetes at recruitment. Overall, this study showed high acceptability of CGM sensor use during pregnancy. The CGM feedback motivated users in the unblinded group to track their daily behaviours through accessing information that they found relevant and of value. There was an overall higher satisfaction rate in the users of the unblinded group with a lower percentage of users reporting adverse events – the most common being skin reactions, such as erythema, and/or itching and pain at the sensor insertion site.

The strengths of our trial include its longitudinal design to capture glucose data throughout pregnancy from the first to the third trimester, and the long CGM wear time of up to 14 days which provides a better capture of free-living glycaemic variability. However, our trial has limitations, the current recruited sample size in this pilot RCT might not have sufficient power to provide a conclusive answer to our primary hypothesis despite achieving our minimum recruitment number of 60 participants in each study arm based on the rule of thumb for pilot RCTs[20]. This also makes our study findings less generalizable, and would require replication with a larger sample size. We have also noted that patients might have benefited from better CGM education and personalized guidance on the interpretation of the glucose readings obtained to be better able to make suitable lifestyle adjustments to further improve glycaemic control. Furthermore, although efforts were made to ensure compliance to CGM scans in the unblinded group users, almost half failed to provide complete CGM data.

CONCLUSIONS

CGM feedback have the potential to offer pregnant patients a way to monitor their glucose levels during pregnancy, allowing improvement in glucose control through behavioural change and reducing the risk of developing GDM. Future trials of a larger sample size coupled with better education and guidance by health care professionals regarding the use and interpretation of the glucose sensor readings are required for better clinical outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

Author contribution

P.L.Q. contributed to the design of the study, the statistical analysis and the writing of the manuscript. K.H.T., L.K.T., L.N., S.T., B.S.M.C., A.W., S.P.T.T. and S.B.A. contributed to the conceptualization of the study. K.H.T. was responsible for the funding acquisition for this study. P.L.Q., K.H.T., L.K.T., L.N., S.T., B.S.M.C., A.W., S.P.T.T., and S.B.A. were responsible for finalizing the manuscript. All authors contributed to and approved the final manuscript.

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