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Continuous Glucose Monitoring Feedback in the Subsequent Development of Gestational Diabetes: A Pilot, Randomized, Controlled Trial in Pregnant Women

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Abstract

Objective This study evaluated the effects of receiving glucose feedback from continuous glucose monitoring (CGM) by intermittent scanning (unblinded group), and CGM with masked feedback (blinded group) in the subsequent development of gestational diabetes mellitus (GDM).

Study Design This was a prospective, single-center, pilot, randomized controlled trial including $n = 206$ pregnant women in the first trimester of pregnancy with no prior diagnosis of type 1 or type 2 diabetes. The participants were randomized into the unblinded group or blinded group and wore the CGM in the first trimester of pregnancy (9–13 weeks), the second trimester of pregnancy (18–23 weeks), and late-second to early-third trimester (24–31 weeks). The primary outcome was GDM rate as diagnosed by the 75-g oral glucose tolerance test (OGTT) at 24 to 28 weeks.

Results Over 47 months, 206 pregnant women were enrolled at 9 to 13 weeks. The unblinded group had a higher prevalence of women who developed GDM (21.5 vs. 14.9%; $p > 0.05$), compared to the blinded group. In the unblinded group compared to the blinded group, plasma glucose values were higher at 1 hour (median 7.7 [interquartile range {IQR}: 6.3–9.2] vs. 7.5 [6.3–8.7]) and 2 hours (6.3 [5.8–7.7] vs. 6.2 [5.3–7.2]), but lower at 0 hour (4.2 [4.0–4.5] vs. 4.3 [4.1–4.6]; $p > 0.05$). All these differences were not statistically significant.

Conclusion Glucose feedback from CGM wear in the first to the third trimester of pregnancy without personalized patient education failed to alter GDM rate.

Keywords
- pregnancy
- continuous glucose monitoring
- gestational diabetes mellitus
- pilot trial

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Key Points

- Continuous glucose monitoring (CGM) is feasible for use in pregnant women.
- No significant difference in gestational diabetes rates with or without CGM feedback.
- Future clinical trials should incorporate CGM education and personalized guidance to enhance study outcomes.

Pregnant women diagnosed with gestational diabetes mellitus (GDM) were shown to have higher glycemic variability (GV) which refers to fluctuations in blood glucose, compared to non-GDM women.[1] GV metrics of higher mean and standard deviations (SDs) in glucose levels[2–4] and a greater mean amplitude of glycemic excursion (MAGE),[2,4] were observed in women who developed GDM compared to those who did not.[1] Since the size and duration of these glucose fluctuations throughout the day govern the overall daily glycemic control,[5] it suggests that better glycemic control to prevent blood glucose fluctuations during pregnancy may be pertinent in lowering the risk for GDM development.

The American Diabetes Association recommends the use of self-monitoring of blood glucose as the primary measure of glycemic control during pregnancy,[6] and continuous glucose monitoring (CGM) is a way of objectively, accurately, and painlessly measuring these blood glucose variations.[1,7,8] Previous studies on CGM use in pregnancy were based on earlier versions of CGM sensors that required calibration,[9] masked the glucose readings,[10,11] and only had a sensor-life of 3[10,11] to 6 days.[9,12] In September 2016, the U.S. Food and Drug Administration approved the Freestyle Libre Pro Glucose Monitoring System, a calibration free-continuous glucose monitoring 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 health care 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 are available for clinical evaluation.[13] 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 are not visible during the time of application. Patients using the Freestyle Libre can receive CGM glucose value feedback any time by intermittently scanning the sensor.[14]

A meta-analysis has demonstrated that lifestyle interventions such as diet and physical activity was successful in preventing GDM,[15] possibly through improved glycemic outcomes.[16] Evidence in the form of randomized controlled trials (RCTs) and cohort studies suggests that glycemic control can be better managed with glucose value feedback from CGM during pregnancy.[17–20] The ease of interpretation of the glucose readings from the CGM can empower, and serve as an educational tool for patients to better manage their glucose levels during pregnancy through lifestyle changes.[1,8,19] Moreover, better glycemic control has overall led to improved obstetric and neonatal outcomes, in studies involving pregnant women with type 1 diabetes,[20] type 2 diabetes,[17] and gestational diabetes.[1] However, all the randomized trials to date have been conducted in patients with diabetes[17,18,20] who are already highly motivated to improve their glycemic control. So far, no studies have been conducted in pregnant women without diabetes, or to associate CGM glucose feedback in these pregnant women with GDM development.

To our knowledge, our study is the first to evaluate the benefits of CGM glucose value feedback throughout pregnancy in women without preexisting type 1 diabetes or type 2 diabetes. The primary aim of this RCT study was to compare GDM rates and plasma glucose levels from the oral glucose tolerance test (OGTT) between users receiving CGM glucose value feedback (unblinded) and those who were not (blinded). The secondary aim was to compare maternal glycemic control, and GV 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 glucose value feedback will result in lower OGTT glucose values, and a lower GDM rate (primary outcome) with improved glycemic control and GV parameters throughout pregnancy (secondary outcome).

Materials and Methods

Study Design

The Integrating the Use of Calibration-Free Continuous Monitoring for Pregnancy Glucose Profiling (I-PROFILE) study was a prospective, single-center, pilot, and feasibility RCT conducted at the Department 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 Centralized 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 registration number NCT05123248) and summarized below. The data that support the findings from this study are available from the corresponding author upon request. Consolidated Standards of Reporting Trails (CONSORT) reporting guidelines were used in the reporting of the study findings.[21]

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 in a 1:1 ratio: The unblinded group received the Freestyle Libre CGM sensor (Abbott Diabetes Care, Alameda, CA), and the blinded study group received the Freestyle Libre Pro CGM sensor (Abbott Diabetes Care, Alameda, CA). 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 preexisting chronic diseases, including kidney disease and pregestational diabetes.

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 nonblinded 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 which is the CGM with glucose value feedback (Freestyle Libre), or the blinded group which is the CGM with masked feedback (Freestyle Libre Pro). The flow of the study clinic visit schedule is shown in ►Supplementary Fig. S1 (available in the online version). There were four scheduled clinic appointments for all participants, and GDM was routinely screened between 24 and 28 weeks with the 75-g 3-point OGTT[22] (►Supplementary Fig. S1, available in the online version).

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 overbandage for up to 14 days at every clinic visit in the first trimester of pregnancy (9–13 weeks), the second trimester of pregnancy (18–23 weeks), and late-second to early-third trimester (24–31 weeks). The CGM would record an interstitial glucose reading every 15 minutes. 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. 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. They 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. Participants in this group received instructions on how to scan the device every 8 hours and to observe the glucose range to be between 3.5 and 10 mmol/L. At the end of the 14 days, participants were to scan the sensor using the blinded reader by themselves or they were assisted by a clinical research coordinator in the clinic, and the data from the reader were downloaded to a research computer. 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 (►Supplementary Fig. S1, available in the online version). 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

Participants underwent a 75-g OGTT at 24 to 30 weeks' gestation; fasting glucose (FG), 1-hour plasma glucose (1hPG), and 2-hour 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 criteria: if any one of the plasma glucose values was at or above the following thresholds: 5.1 mmol/L for fasting plasma glucose, 10.0 mmol/L 1hPG, and 8.5 mmol/L for 2hPG.

Secondary Outcome: Analyses of Continuous Glucose Monitoring Data

Data from the CGM were 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, SD, percentage coefficient of variation (%CV), and MAGE. The percentage of time in target ranges were defined as %TIR (3.5–7.8 mmol/L), %TAR (>7.8 mmol/L), and %TBR (<3.5 mmol/L) and were used to assess glycemic control.[13] MAGE quantifies major swings of glycemia and excludes minor ones, was and is considered the gold standard for assessing intraday GV,[23] along with SD and %CV. Extracted CGM data were 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 semistructured 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 to 33 weeks of pregnancy, except for participants who were diagnosed with GDM, who completed the questionnaire at the sixth clinic visit at 6 to 12 weeks' postpartum (►Supplementary Fig. S1, available in the online version).

Maternal Data Collection

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

Statistical Analysis

This study is the first RCT pilot study using CGM sensors in pregnant women comparing a group with CGM feedback and a group without. The actual value of standardized 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.[24]

The analyses were conducted on the intention-to-treat principle which includes all the women who participated in the randomization and completed the study (►Fig. 1). Categorical variables were summarized by counts and proportions; continuous variables data were summarized by means and SD, or by median and IQR in the case of deviations from the normal distribution. The primary analysis used multivariable Poisson regression to assess the associations between the two study arms (unblinded and blinded) with GDM rate, 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 prepregnancy BMI with the variance-covariance matrix of the estimators (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 (►Fig. 1). These participants would have had to wear the CGM sensors at the four timepoints: first trimester at 9 to 13 weeks, the early-second trimester at 18 to 23 weeks, late-second to early-third 24 to 28 weeks, and the third trimester at 32 to 33 weeks (►Supplementary Fig. S1, available in the online version). 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 rate, gestational age of CGM application, and prepregnancy 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 (►Fig. 2). A two-sided p-value <0.01 is considered statistically significant to account for multiple comparisons in the analysis, and p-value <0.1 were described as nonstatistical significant trends. All analyses were performed by using the statistical software STATA 13.1.

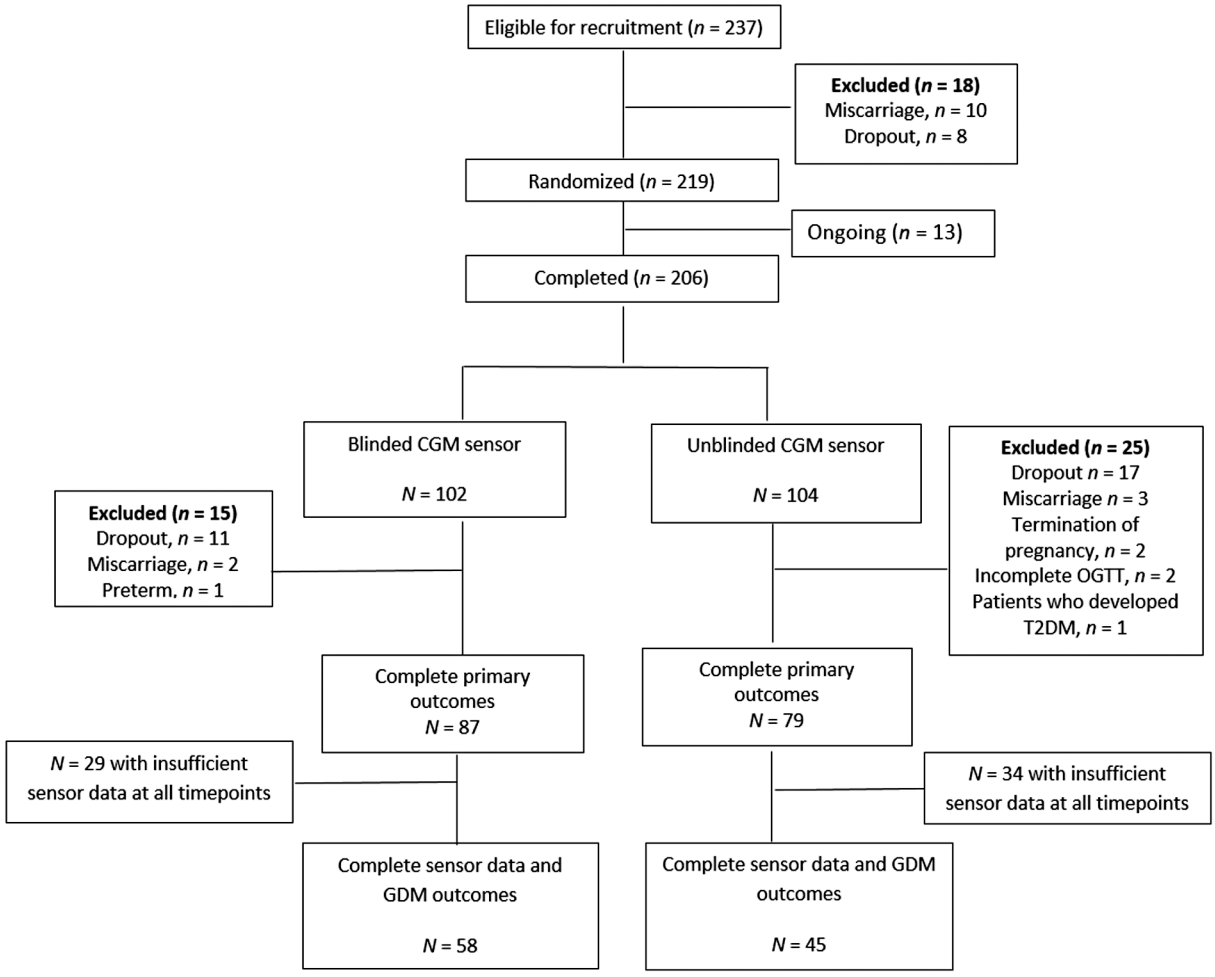

Fig. 1 Study participants flow chart. CGM, continuous glucose monitoring; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

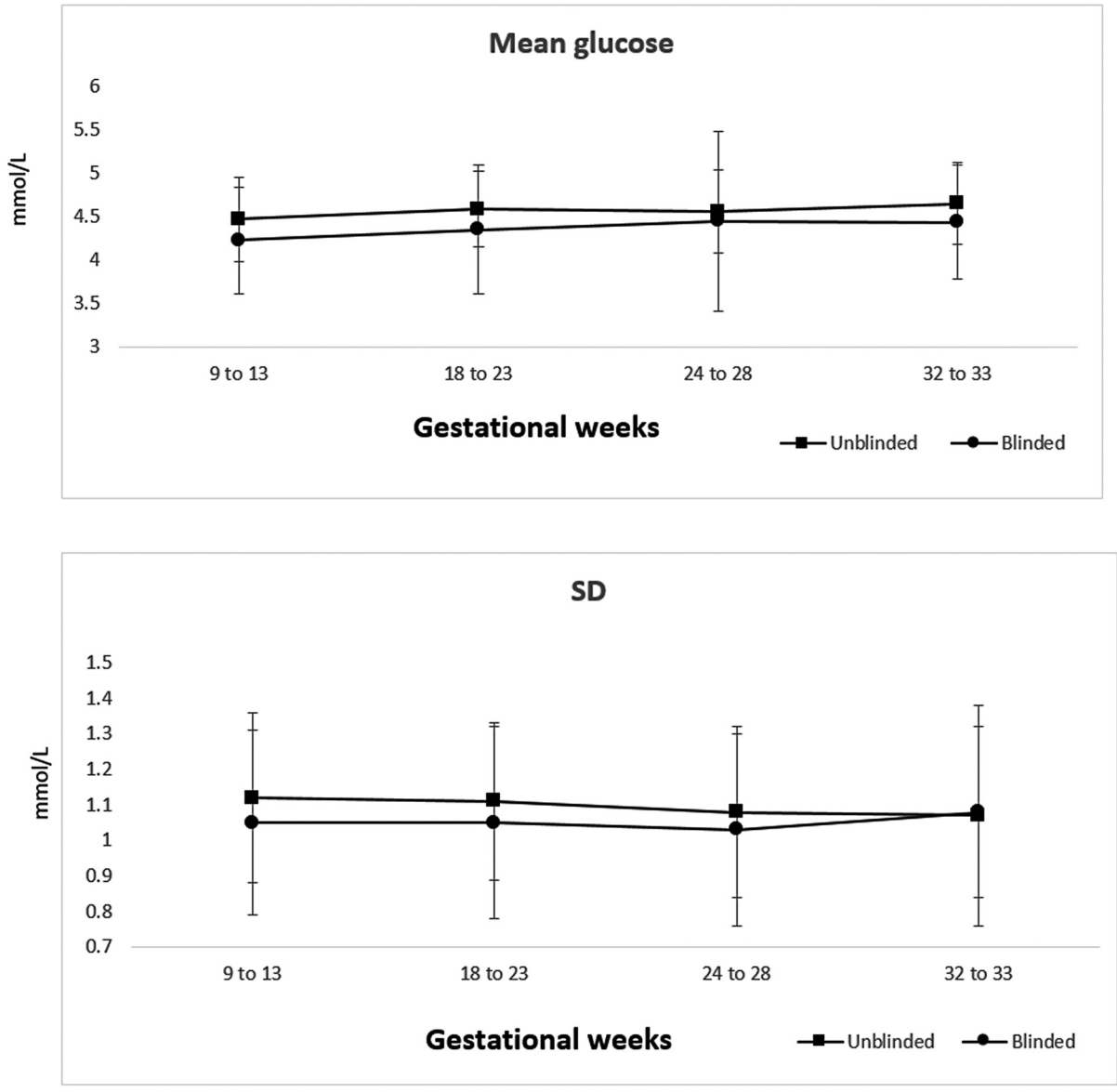

Fig. 2 Trends in mean glucose and glycemic variability parameters (SD, MAGE, and %CV) across the three trimesters of pregnancy by CGM group. CV, coefficient variation is expressed in mean ± SD. There were no statistically significant differences between the glycemic variability parameters in the unblinded and the blinded groups. %CV, percentage coefficient of variation; CGM, continuous glucose monitoring; MAGE, mean amplitude of glycemic excursion; SD, standard deviation.

Results

Baseline Characteristics

Between December 2018 and November 2022, 931 patients were screened and 712 were not eligible because of the following reasons: (1) did not meet the study inclusion criteria ($n = 225$) and (2) declined study participation ($n = 469$). Out of the $n = 237$ eligible participants that were recruited, $n = 8$ dropped out of the study before the randomization and $n = 10$ had a miscarriage and were excluded from the study. Finally, out of the $n = 219$ participants who were randomized into the two study arms, $n = 206$ completed the study (►**Fig. 1**).

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 prepregnancy 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 (►**Supplementary Table S1**, available in the online version).

Primary Outcomes

The differences between the GDM rate and OGTT plasma glucose concentration values in both study arms are shown in ►**Table 2**. There were no significant differences in the

Table 1 Baseline characteristics of participants randomized to the blinded ($n = 102$) and unblinded ($n = 104$) groups

Maternal characteristics[a] ($n = 206$)	Blinded ($n = 102$)	Unblinded ($n = 104$)	*p*-Value
Ethnicity, *n* (%)			0.89
Chinese	62 (60.8)	65 (62.5)	
Malay	31 (30.4)	29 (27.9)	
Indian	4 (3.9)	6 (5.8)	
Others	5 (4.9)	4 (3.8)	
Education, *n* (%)			0.44
Secondary and below	11 (10.8)	8 (7.7)	
College and above	91 (89.2)	96 (92.3)	
Smoking			
Never smoked	76 (74.5)	81 (77.9)	0.83
Ex-smoker	22 (21.6)	20 (19.2)	
Smoking during pregnancy	4 (3.9)	3 (2.9)	
Parity			0.45
Nulliparous	38 (37.3)	44 (42.3)	
Multiparous	64 (62.7)	60 (57.7)	
Family history of diabetes, *n* (%)	48 (47.1)	51 (49.0)	0.78
Age (years), mean ± SD	31.2 ± 4.3	31.5 ± 4.2	0.54
%Prepregnancy BMI (kg/m^2), median (IQR)	22.4 (19.6–26.3)	22.3 (20.95–26.2)	0.42
Gestational age at recruitment (gestational weeks), mean ± SD	11.1 ± 1.3	11.1 ± 1.2	0.84
OGTT assessment (gestational weeks), mean ± SD	25.7 ± 3.5	25.3 ± 4.1	0.53

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; IQR, interquartile range; OGTT, oral glucose tolerance test; SD, standard deviation.
Continuous variables were expressed as mean ± SD. The *p*-value significance is set at $p < 0.05$.
[a]Missing data: prepregnancy BMI ($n = 6$).

Table 2 Gestational diabetes outcomes and oral glucose tolerance test plasma glucose concentrations by study group

	Blinded ($n = 87$)	Unblinded[a] ($n = 79$)	Adjusted *p*-value
GDM			0.37
Yes, *n* (%)	13 (14.9)	17 (21.5)	
No, *n* (%)	74 (85.1)	62 (78.5)	
GDM, RR (95% CI)	1.0 (ref)	1.49 (0.70 to 3.18)	0.30
Plasma glucose concentrations			
Fasting, mmol/L, median (IQR)	4.3 (4.1–4.6)	4.2 (4.0–4.5)	0.48
1-hour, mmol/L, median (IQR)	7.5 (6.3–8.7)	7.7 (6.3–9.2)	0.38
2-hour, mmol/L, median (IQR)	6.2 (5.3–7.2)	6.3 (5.8–7.7)	0.15
Fasting, mmol/L, β (95% CI)	1.0 (ref)	−0.07 (−0.35 to 0.21)	0.62
1-hour, mmol/L, β (95% CI)	1.0 (ref)	0.37 (−0.37 to 1.10)	0.33
2-hour, mmol/L, β (95% CI)	1.0 (ref)	0.45 (−0.14 to 1.04)	0.13

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; CI, confidence interval; GDM, gestational diabetes mellitus; IQR, interquartile range; OGTT, oral glucose tolerance test; RR, relative risk.
Data are presented in frequency (percentage), followed by RR (95% CI) or median (IQR), followed by β-coefficient (95% CI). Results were assessed in 87 participants in the blinded and 79 participants in the unblinded CGM group with available OGTT results; adjusted *p*-values and RR (95% CI) are from Poisson regression (GDM outcomes), and β-coefficient (95% CI) are from linear regression (plasma glucose concentrations) on available data, adjusted for maternal age, ethnicity, education, family history of diabetes, and prepregnancy BMI.
[a]Data missing for OGTT plasma glucose concentrations ($n = 1$).

proportion of pregnant women diagnosed with GDM in the unblinded group compared to the blinded groups (21.5 vs. 14.9%; relative risk [95% confidence interval] 1.49 [0.70–3.18], $p > 0.05$). There were also no significant differences in the FG, 1hPG, and 2hPG of participants in the unblinded group, compared to the blinded 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, $p = 0.38$; 2hPG: 6.3 [5.8–7.7] vs. 6.2 [5.3–7.2] mmol/L, $p = 0.15$). Adjustments were made for covariates such as maternal age, ethnicity, education, family history of diabetes, and prepregnancy BMI.

Secondary Outcomes

The CGM parameters between the unblinded and blinded groups across the three trimesters of pregnancy that represent glycemic control (%TIR, %TAR, and %TBR) are presented in ►Fig. 2, and parameters including mean glucose and GV (SD, MAGE, and %CV) are presented in ►Fig. 2. There were trends of higher %TIR in the first trimester (83.2% [74.1–93.9] vs. 78.1% [58.9–87.1]; $p = 0.06$), third trimester (90.2% [77.9–95.8] vs. 79.5% [65.1–90.4]; $p = 0.07$), and the early-second trimester of pregnancy at 18 to 23 weeks (88.7% [76.4–92.7] vs. 80.5% [59.6–90.4]; $p = 0.02$), compared to the blinded group users. 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]; $p = 0.05$; ►Fig. 2 and ►Supplementary Table S2, available in the online version). There were no significant differences between the unblinded and blinded groups for %TAR, mean, SD, MAGE, and %CV levels (►Fig. 2).

Acceptability and Satisfaction from Continuous Glucose Monitoring 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 behaviors (92.0 vs. 75.6%, $p = 0.006$), compared to participants in the blinded group (►Supplementary Table S3, available in the online version). 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%, $p = 0.002$; ►Supplementary Table S3, available in the online version). 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 (►Supplementary Table S4, available in the online version). Among the users in the unblinded group, 82.2% reported that they would scan their sensors at 4- or 8-hour intervals, and 36% reported that they never missed a scan. Approximately 57.5% were not motivated to change their lifestyle behaviors and 83.6% never correlated their meal intake with use of the sensor (►Supplementary Table S5, available in the online version).

Discussion

This prospective pilot RCT study has demonstrated the feasibility of CGM use in pregnant women. However, the participants in the unblinded group did not show any significant differences in the primary outcomes of GDM rate of development, and OGTT plasma glucose concentrations. In contrast, we observed a higher proportion of those who developed GDM in the unblinded group (21.5%), compared to blinded group users (14.9%). There were no significant differences seen in the %TIR, %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 preexisting type 1 or type 2 diabetes, early in pregnancy before the diagnosis of GDM. Our study did not show a reduction in GDM rate between the unblinded group over the blinded group users. The null associations with GDM rate were also reflected by the null associations in the plasma FG, 1hPG, and 2hPG levels between the two study arms. 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 Continuous glucose monitoring 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 hyperglycemia as mothers spent more time within their target glucose range.[20]

Direct comparisons to the CONCEPTT study are difficult due to the fundamental differences in study design. The CONCEPTT study recruited pregnant women who were diagnosed with diabetes in whom careful monitoring of glucose levels was 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 intervals of 6 to 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 glycemic 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 to inform them of the out-of-range glucose values.[25] 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. There could be a benefit of utilizing CGM devices which provide real-time

glucose readings without needing the scan the sensor to obtain glucose readings.[26] Furthermore, participants in the unblinded group from our study did not receive thorough education on managing diet or physical activity through the feedback received from the CGM to achieve clinically relevant improvements in glucose control.[27]

Our study suggests a nonsignificant trend of improved glycemic control throughout the pregnancy as seen from a trend of higher %TIR in the unblinded group. There was also trend of lower %TBR in the unblinded group during the first and early-second trimesters. The CONCEPTT study reported improved glycemic control parameters in a group receiving glucose values via CGM feedback compared to those without at 34 weeks' gestation[20] when they observed a reduced percentage of women who spent time above the target glucose range,[20] but with no significant differences in time below target range. These discrepancies in findings are mainly attributed to the population of women with non-type 1 or type 2 diabetes in our study sample. GDM and non-GDM pregnant patients had mild hyperglycemia, and higher incidences of hypoglycemia compared to patients with type 1 or type 2 diabetes.[28] 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 and 2%, as most of the women in this sample were healthy and less likely to be hyperglycemic.

There were no differences in the mean glucose, SD, %CV, and MAGE values, except for the nonsignificant trend of higher mean concentrations in the unblinded group at the timepoints (9–13 and 18–23 weeks). In contrast to our study, the CONCEPTT study reported significantly reduced glucose SD, lower MAGE, and nonsignificantly reduced glucose coefficient of variation, suggesting less GV and better glycemic control in the users of the unblinded real-time CGM group.[20] 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[29] compared to the real-time CGM. Our observations suggest that participants in the unblinded group were more motivated to use the sensor for tracking their daily behaviors. However, despite this, the self-reported data showed that 57.5% of participants in this group did not modify their diet nor physical activity level despite receiving CGM feedback. Future studies examining CGM feedback in pregnant patients who are healthy at the time of recruitment should be coupled with patient education and personal guidance to achieve better glycemic control and GV CGM parameters.[27]

Our study is the first to conduct a pilot RCT comparing CGM with glucose value feedback and without in healthy pregnant women without type 1 or 2 diabetes at recruitment. Similar to previous a published study by Di Filippo et al,[30] our study had the CGM applied on women during pregnancy who were due for or had completed their OGTTs. The main limitation was the compliance to the scanning of the device every 8 hours, and occasional complaints of the discomforts brought on by the sensor wear which was not too dissimilar from previously published work.[30,31] 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 behaviors through accessing information that they found relevant and valuable. 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 GV. However, our pilot trial has limitations that need to be addressed. The current recruited sample size was not sufficiently powered 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.[24] Furthermore, the pilot study's results unexpectedly showed a higher rate of GDM among participants in the unblinded group, contrary to our initial hypothesis. Due to this unexpected finding, we decided against extending the study to enroll more participants. We have also noted that the current study design could be improved, firstly by providing CGM education and personalized guidance on the interpretation of the glucose readings to be able to make suitable lifestyle adjustments to further improve glycemic control. Secondly, inserting the CGM device during the first trimester (9–13 weeks) of pregnancy may not provide enough time for behavioral changes and glycemic control improvements. Future studies could explore using CGM sensors to improve glycemic control even earlier during the preconception period for potentially better outcomes. Lastly, although efforts were made to ensure compliance to CGM scans in the unblinded group users, almost half failed to provide complete CGM data which might have reduced the overall effectiveness of the study.

Conclusion

In summary, this pilot RCT demonstrated the feasibility of CGM sensor use during pregnancy, but was unable to conclude an effect of the unblinded CGM on GDM rates.

Note

Date of registration: November 17, 2021
Date of initial participant enrolment: October 16, 2018
Clinical trial identification number: NCT05123248
URL of the registration site: https://clinicaltrials.gov/ct2/show/NCT05123248?term=I-Profile&draw=2&rank=1

Authors' Contributions

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., N. L., 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., N.L., 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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Conflict of Interest
None declared.

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