TITLE PAGE

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Continuous Glucose Monitoring Results in Lower HbA1c in Malaysian Women with Insulin Treated Gestational Diabetes: A Randomized Controlled Trial

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CGM lowers HbA1c in Malaysian women with insulin treated GDM: An RCT

AUTHORS:

Dr SS Paramasivam, MRCP(UK); Lecturer in Internal Medicine and Endocrinology, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr K Chinna, PHD; Associate Professor, Department of Social and Preventive Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr AKK Singh, MMedSc (Mal); Internal Medicine Physician, Department of Medicine, Serdang Hospital, Selangor, Malaysia.

Dr J Ratnasingam, MMedSc(Mal); Lecturer in Internal Medicine and Endocrinology, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr L Ibrahim, MMedSc(Mal); Lecturer in Internal Medicine and Endocrinology, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr LL Lim, MRCP(UK); Lecturer in Internal Medicine and Endocrinology, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr ATB Tan, MRCP(UK); Associate Professor in Internal Medicine and Endocrinology,, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr SP Chan, FRCP(Edin); Visiting Professor in Internal Medicine and Endocrinology,, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr PC Tan, MRCOG (UK); Professor in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Dr SZ Omar, MMedSc(Mal); Professor in Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

Prof RW Bilous, FRCP; Professor of Clinical Medicine and Dean of Clinical Affairs, Newcastle University Malaysia (NUMed), Johor, Malaysia.

Dr SR Vethakkan, MMedSc(Mal); Associate Professor in Internal Medicine and Endocrinology,, Department of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia.

CORRESPONDING AUTHOR:

Dr Sharmila S Paramasivam; sharmsp13@gmail.com

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Novelty statements:

- Our study participants had gestational diabetes treated with insulin thus representing women with more severe disease with higher risk for adverse materno-fetal outcomes.

- We showed that the use of continuous glucose monitoring in women with GDM on insulin improved glycemic control with no significant increase in symptomatic hypoglycaemia.

- CGM may have a role in improving glycaemic control in gestational diabetes on insulin, which in turn could result in better materno-fetal outcomes.

- This could have important clinical implications in management, especially when gestational diabetes occurs at a higher rate in Asia

ABSTRACT

Background: Good glycaemic control in gestational diabetes mellitus (GDM) improves pregnancy outcomes and reduces perinatal morbidity. Continuous glucose monitoring (CGM) improves HbA1c and pregnancy outcomes in pre-gestational diabetes, however its role has not been established in GDM.

Objective: To determine if therapeutic, retrospective CGM improves HbA1c with less hypoglycaemia in insulin treated women with GDM.

Methods: This prospective, randomized-controlled, open-label trial enrolled 50 insulin-treated GDM mothers randomized to either retrospective-CGM (6-day-sensor) at 28, 32, and 36-weeks gestation (Group-1, CGM, n=25) or usual antenatal care without CGM (Group-2, control, n=25). All women performed 7-point capillary blood glucose (CBG) profiles at least 3-days per week and recorded hypoglycaemic events (symptomatic and asymptomatic CBG <3.5mmol/L; non-fasting <4.0mmol/L). HbA1c was measured at 28, 33 and 37-weeks. In Group-1, both CGM and CBG data were used to manage diabetes, while Group-2 mothers were managed based on CBG data alone.

Results: Baseline characteristics (age, pre-pregnancy BMI, HbA1c, total insulin dose) were similar between groups. There was a lower increase in HbA1c from enrolment at week 28 until 37 weeks

gestation in CGM mothers (ΔHbA1c: CGM +1mmol/mol (0.09%), control +3mmol/mol (0.30%), p=0.024. Mean HbA1c remained unchanged throughout trial duration in the CGM group, but rose significantly in controls as pregnancy advanced. Mean HbA1c in the CGM group was lower at 37 weeks compared with controls (33±4mmol/mol (5.2±0.4%) vs 38±7mmol/mol (5.6± 0.6 %), p<0.006. 92% of CGM mothers achieved an HbA1c ≤39mmol/mol (≤5.8%) at 37-weeks compared to 68% of controls (p=0.012). Neither group experienced severe hypoglycaemia.

Conclusion: CGM use may be beneficial in insulin-treated GDM as it improves HbA1c compared with usual antenatal-care without increasing severe hypoglycaemia.

Keywords: Gestational Diabetes Mellitus, GDM, Continuous-Glucose-Monitoring, CGM, HbA1c

BACKGROUND

Gestational diabetes mellitus (GDM) is defined as glucose-intolerance of variable severity with onset or first recognition during pregnancy and is associated with a higher frequency of adverse materno-fetal outcomes[1] . The incidence of GDM is increasing globally. Asian ethnicity is emerging as a recognized risk factor, with prevalence rates as high as 11.4% in Malaysia and 14% in South India [2,3]. Poor glycaemic-control in GDM has been demonstrated to increase perinatal mortality/morbidity rates[4].Treatment of GDM has been shown to reduce serious perinatal-complications, and perinatal-outcomes are significantly improved with better glycaemic-control[4,5]. In particular, intensive treatment of GDM reduces macrosomia. Crowther et al reported a reduction from 21% (no treatment) to 10% (treatment) [5] while Landon et al[4] demonstrated that achieving blood-glucose targets of 5.3mmol/L(fasting) and 6.7mmol/L(2-hours postprandial) results in a macrosomia-rate of 5.9% compared with 14.3% in the control arm.

CGM advantages include the ability to monitor nocturnal-glucose levels and detect post-prandial hyperglycaemic excursions which are the blind-spots of conventional capillary blood glucose (CBG) monitoring[6,7].Both real-time and closed CGM use in non-gravid women with Type 1 Diabetes Mellitus (T1DM) has been shown to improve glycaemic-control and reduce hypoglycaemia [8,9,10,11]

In pregnancies complicated by diabetes, where tight glucose-control is necessary to improve materno-fetal outcomes, CGM may have a role in fine-tuning management and achieving recommended targets recommended as it provides comprehensive 24-hour glucose-profiles encompassing post-prandial glucose excursions [12], as well as details of average time-spent-in-hypoglycaemia, euglycaemia and hyperglycaemia for periods of 3-6 days, in comparison with 4–8 point ~~capillary blood glucose (~~CBG~~)~~ profiles[13]. A trial of retrospective CGM in women with

pre-gestational diabetes by Murphy et al, demonstrated that those who received CGM during pregnancy had better glycaemic control with lower HbA1c and reduced macrosomia risk compared to women who received regular antenatal care [14]. The recently published CONCEPTT trial also demonstrated improved neonatal outcomes in women with type 1 diabetes who used real-time CGM [15]. The American Association of Clinical Endocrinologists (AACE) currently recommends CGM use in pregnant women with T1DM[16]. Several groups, in mainly observational studies, have demonstrated CGM's diagnostic efficacy in detecting hyperglycaemia and hypoglycaemia missed by conventional CBG testing in women with GDM [6,7,12,17], while others have demonstrated CGM use leads to changes in clinical decision making[6,12,18]. Yu et al have shown that periodic 72-hour retrospective CGM use in women with diet-controlled GDM (the majority of whom were were still on diet alone by trial end) improves pregnancy outcomes when compared with a control group of mothers using CBG monitoring alone[19]. This interventional study however, did not report HbA1c outcomes.

To our knowledge, there have been no published trials on the efficacy of retrospective CGM in exclusively insulin-treated women with GDM, specifically examining glycaemic outcomes such as HbA1c and hypoglycaemia during longitudinal follow-up until delivery. We therefore designed an open-label randomized controlled trial to evaluate prospectively ~~evaluate~~ the therapeutic effect of retrospective CGM use in insulin-treated women with GDM. We hypothesized professional CGM use at 4-week intervals in the second-half of pregnancy would improve glycaemic control and reduce hypoglycaemia.

METHODOLOGY

This prospective, open-label, randomized controlled trial enrolled 57 insulin-treated women with GDM (Figure1) receiving multi-disciplinary team care from consultant obstetricians, endocrinologists, dietitians and diabetes nurse educators between April 2013-April 2015 at a tertiary care antenatal-clinic in Kuala Lumpur, Malaysia. The study was approved by the local ethics committee (Medical Research Ethics Committee of University of Malaya Medical Centre) and the women provided informed, ~~-~~written consent.

The inclusion and exclusion criteria are stated in Table 1. Our centre practises opportunistic universal screening during the 1st encounter with the obstetrician with a 75g-OGTT using diagnostic criteria of a fasting plasma glucose ≥5.1 and/or a 2 hour post load plasma glucose of ≥7.8mmol/L as per local guidelines. If an early screen is negative patients are re-screened at 24-28 weeks gestation.

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The main exclusion criteria were pre-gestational T1DM/T2DM or newly diagnosed overt-diabetes in pregnancy (HbA1c ≥48mmol/mol (6.5%), fasting glucose ≥7.0mmol/L, random glucose ≥11.1mmol/L).

Study protocol

All participants ~~gave fully informed consent and~~ were randomized in blocks of 4 using sealed envelopes into 2 groups (25 women per group) by a research assistant. The participants randomly chose one of 4 sealed envelopes with the treatment-allocation within, those who withdrew were replaced by eligible women who consented to participate and were then randomized in the same manner i.e. blocks of four. Six~~6~~ women randomized into the CGM group withdrew voluntarily

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~~even~~ before the start of the study and did not undergo~~t have any~~ CGM ~~done~~. They were replaced by another 6 participants selected randomly. 1 participant withdrew within the first CGM, hence she was replaced by another participant also selected randomly. Reasons for withdrawal were religious beliefs, inability to commit to the scheduled appointments and inconvenience of wearing CGM.

Baseline demographic, anthropometric and clinical information were obtained via interview using a structured-questionnaire. Every effort was made to provide equal-care and education to both groups. Group-1 underwent CGM at 28, 32 and 36-weeks gestation in addition to standard antenatal-care while Group-2 received only standard antenatal-care. CGM-group women were managed based on CGM and CBG data, while controls were managed based on CBG alone. Participants enrolled in both arms were required to measure CBG seven times per day (fasting,pre- and 2hours post-prandial, pre-bed) at least 3 days per week. In addition, in order to calibrate the CGM-device, those in Group-1 had to monitor CBG a minimum of 4 times per day during the 6 days of sensor-use. All participants were taught by trained diabetes-nurse-educators to self-monitor blood-glucose and those receiving CGM were given additional training on how to use the CGM. All participants in both groups were taught to record meals, CBG values, hypoglycaemic events, insulin timing and dosage, and exercise in standardized log-sheets. As per standard in our centre, women with GDM are reviewed weekly if glucose levels are off-target and 2-weekly if within target until 36-weeks-gestation. After 36-weeks, all women are reviewed weekly until delivery.

Similar glycaemic targets for GDM (standard of care in our centre) were used in both groups: fasting 3.5 – 5.0mmol/L, pre-meals 4.0 – 5.8mmol/L, 2-hours post-prandial 4.0 - 6.7mmol/L~~l~~. However in the CGM group, an additional target of 1-hour postprandial <.7.8 mmol/L~~l~~ on CGM

was also used. In all participants, CBG, food-diaries and hypoglycaemia-logs were collected and reviewed at each visit. They were asked at every visit about any hypoglycaemic events that were not logged and these were also documented by the researchers. Adjustments were made to therapy if participants did not achieve target glucose despite best efforts at diet-modification. Participants with fasting-glucose<3.5mmol/L and non-fasting glucose<4mmol/L or symptoms of hypoglycaemia (regardless of glucose-level) while on insulin had their insulin-doses reduced accordingly as per standard practice.

The CGM device used was the Medtronic iPro2 Enlite 6-day sensor which measures interstitial fluid glucose within a range of 2.2-22mmol/L. The sensor was inserted over the abdomen on Day-1 and removed Day-7. During this period CGM glucose measurements were not accessible to the women or management-team.

In the group that underwent CGM, after sensor removal (Day-7) at weeks 29, 33 and 37, stored CGM-data were downloaded using the manufacturer's software (Carelink iPro-Therapy Management Software) and printed reports were given to both participant and doctor the same day. The CGM-data were reviewed by the endocrinologist on the day of removal, and findings discussed with participants, taking note of abnormal glycemic -patterns. They were advised to identify any possible reasons for these patterns, and their diet, exercise as well as insulin-dose were taken into consideration. The CGM-data together with CBG results were used to make therapeutic decisions.

While for the purpose of data-analysis, euglycaemia ~~on CGM~~ was defined as glucose at any time-point within the range 3.5–6.7mmol/L, however therapeutic decision-making was modified based upon an upper limit postprandial target of 7.8mmol/L at 1hour and not 6.7mmol/L.

HbA1c was measured in all women at week-28, 33 and 37. The HbA1c assays were DCCT-aligned and IFCC/NGSP-certified. Other parameters such as weight and urine ketones were monitored at every visit. All women had fetal ultrasound-scans at regular intervals as decided by the obstetrician. Fetal parameters were monitored and plotted on customized local fetal growth charts. Birth-information (mode-of-delivery, maternal complications) as well as neonatal-outcome parameters such as birth-weight, gestational-age at delivery, APGAR score, hypoglycaemia, jaundice and neonatal ICU admission were retrieved from hospital files.

The prespecified primary outcome was change in HbA1c from 28-37 weeks. The secondary outcome was maternal hypoglycaemia.

Power Calculations

Based upon Murphy's research in women with pre-gestational diabetes[14],a minimum sample size of 36 was required to achieve an 80% power to detect a 0.6 % reduction in HbA1c at P=0.05. To allow for attrition, a sample size of 50(25 per group) was decided upon.

Statistical analysis:

SPSS (Statistical Package for the Social Services) IBM version 20.0 software was used for data-analysis. Data are presented as means (±Standard Deviation) (continuous parametric-variables), medians (Q25–Q75)(continuous non-parametric variables) and percentages(categorical-data). Differences between groups were evaluated using t-test and chi-squared-test. Within group differences were evaluated with paired t-testing. Relationships between continuous variables were analyzed using Pearson's correlation-test. Statistical significance threshold was $p< 0.05$.

RESULTS:

Baseline characteristics

A total of 50 women completed the protocol (Figure 1) with 25 randomized to the CGM-arm (Group 1) and 25 to the control-arm (Group 2).

Baseline characteristics were not different between groups except for an earlier gestational age at diagnosis of GDM in the CGM arm (Table 2). Although 60 % (15/25) of women in the CGM arm and 36 % (9/25) in the control-arm had GDM diagnosed before 20 weeks gestation, all women were asymptomatic, had no pre-gravid diagnosis of hyperglycaemia and had a baseline HbA1c < 48mmol/mol (6.5%).

Therapy prior to study enrolment

Duration of metformin therapy and insulin therapy prior to enrolment were not significantly different between groups. Intensification of insulin therapy (change in total daily dose and number of injections) was not different between groups. The frequency of health-care provider contact (dietitian, diabetologist, diabetes educator nurse) was not different between groups prior to study enrolment.(Table 2)

Glycaemic outcomes

Both groups had a similar baseline HbA1c 32±3mmol/mol (5.1±0.3%) vs. 34±6mmol/mol (5.3±0.5%), p=0.124 (Figure 2 and Table 3). As pregnancy advanced, the CGM-group had significantly lower HbA1c levels compared to standard-care at both 33 and 37-weeks (Figure 2 and Table 3). Mean HbA1c remained unchanged throughout trial duration in the CGM-group, but steadily rose in the standard-care-group as pregnancy advanced. Mean change in HbA1c from

baseline (delta HbA1c) was only +1mmol/mol (0.09%) in the intervention-group compared to + 3mmol/mol (0.30%) in standard care (p=0.024). A significantly higher proportion of women with CGM attained HbA1c<40mmol/mol (5.8%) at 37 weeks, compared to standard-care (92 v 68%; p= 0.012). There were no differences in fasting blood glucose and CBG values between groups at any of the time-points (Table-3).

Hypoglycaemia

Throughout the study-period, the majority of women in both groups experienced hypoglycaemia (symptomatic and asymptomatic) at least once after study enrollment, with a numerically greater frequency in the CGM-group which was not significant (92% vs. 72%, p=0.138). Overall hypoglycaemia frequency rates (combined symptomatic and asymptomatic) were significantly higher in the CGM group (Table 4). However there were no significant differences in symptomatic hypoglycaemia per person between groups. There were no episodes of severe hypoglycaemia in either group. Similar findings were seen during the last 4 week period, where there was more hypoglycaemia overall (both symptomatic and asymptomatic biochemical hypoglycaemia) in the CGM-group, but no difference in symptomatic hypoglycaemia alone between groups (Table 4). The majority of these episodes of hypoglycaemia (94.8%) were in the range 3-4mmol/L, 49.5 % of which were asymptomatic.

Insulin therapy

Total-insulin-requirement increased throughout pregnancy in both groups, however the quantum of increase from baseline to study-end did not differ significantly between groups (CGM vs control: 16.2±6.4 vs.11.8±13.6units, p=0.314. Total insulin -dose was also similar in both groups at baseline, 32 and 37 weeks. Numerically more women in the CGM-arm were on intensive insulin-therapy (≥4 injections/day) at study-end (CGM 74% vs. standard-care 56%, p=0.195).

Intensification of insulin therapy was similar in both groups. At pregnancy end, 72% of the CGM mothers were on insulin analogues compared to 52% in the standard care (p=0.057). Both groups had equal numbers of women on metformin (76% in each group) (Table 5)

Frequency of Health-care Provider contact post-enrolment

Post-enrolment, the CGM-group had more visits per person with the physician compared to standard care (8.6±1.5 vs 7.1±1.6 visits per person, p=0.001). Frequency of contact with the diabetologist, dietitian and diabetes educator nurse were not significantly different between groups. (Table 5)

Maternal and fetal outcomes

All women delivered by 38 weeks with the exception of 3 pre-term deliveries from the CGM-group (at 32, 35 and 36 weeks respectively) and one from the control group at 36 weeks. Birth-weight was non-significantly higher in the standard-care group compared with intervention (Table 6).

Continuous Glucose Monitoring

All women in the intervention-arm underwent CGM as scheduled at 3 time-points except for two who had preterm-deliveries at 32-weeks(completed first CGM only) and 35-weeks(completed first and second CGM) respectively. The third patient who had a pre-term delivery at 36 weeks was able to complete her third CGM. As pregnancy advanced, percentage time-in-euglycaemia increased with concurrent reduction in time-in-hyperglycaemia, and there was no significant change in time-spent-in-hypoglycaemia from 1st to 3rd CGM (Table 7). A mean of 21.4 hours/week of hyperglycaemia (glucose>6.7 mmol/L) was detected by the 1st CGM but missed by CBG.

DISCUSSION

We have demonstrated that additional use of continuous glucose monitoring in insulin-treated women with gestational diabetes improves glycaemic control as evaluated by delta HbA1c , when compared with standard antenatal-care with self-monitoring of CBG alone. Delta HbA1c from enrolment at 28 weeks gestation to trial end was significantly lower in the intervention-group compared to standard-care (p=0.024).Over the course of pregnancy, CGM use was associated with a reduced time in hyperglycaemia without increasing time in hypoglycaemia, suggesting that the improvement in glycaemic control as measured by HbA1c was real. At delivery, more GDM mothers who used CGM achieved an HbA1c <40mmol/mol (5.8%) compared to standard-care (92% vs. 68%, p<0.05). This improvement in HbA1c was most likely secondary to a greater awareness of hyperglycaemia in the CGM-arm, leading to greater intensification of insulin therapy by the endocrinologist, and perhaps more intensive diabetes self-management by the women. The CGM sensor detects hyperglycaemia over the entire postprandial-period,in contrast to CBG which evaluates discrete post-meal time-points, thus often missing peak prandial hyperglycaemia. In our study, a mean of 21.4 hours/week of hyperglycaemia (glucose>6.7 mmol/L) was detected by the 1st CGM but missed by CBG. Although mean total-insulin-dose was similar in both groups at delivery, 85.7% CGM mothers versus 40% standard care mothers had treatment intensification (increased number of insulin injections per day from baseline, p=NS), with more CGM women on basal-bolus therapy compared with standard care (p=NS).

There have been a few other randomized-controlled parallel-arm trials evaluating therapeutic, retrospective CGM-use in pregnancy [14,19,20]. To our knowledge, ours is the first to focus

exclusively on insulin-treated women with GDM using the 6-day sensor. Our trial is also the first to report details of concomitant insulin-therapy adjustments with CGM-use and focus on HbA1c outcomes in GDM. Murphy et al, studied higher-risk mothers with pre-gestational diabetes, finding reductions in HbA1c with CGM use which began to emerge at 28-32 weeks with a final difference of 6 mmol/mol (0.6%) resulting in reduced macrosomia rates in the CGM arm[14].These women began CGM use earlier in pregnancy as they had established diabetes, thus undergoing more periods of monitoring (mean: 4.2 times over 24 weeks). Our women however, utilized CGM 3 times over 9 weeks (from 28-weeks gestation), yet demonstrated a significant 4 mmol/mol (0.4%) lowering of HbA1c in the intervention-arm. In contrast, Secher et al evaluated the use of periodic real time CGM in pre-gestational diabetes (Type 1 and 2) finding no differences in pregnancy outcomes, hypoglycaemia and HbA1c compared with standard-care [20]. These women had good glycaemic control similar to the standard care group, thus CGM might not have been able to effect much change. The recently published CONCEPTT trial [15] studied real-time CGM use in 215 type 1 diabetic women recruited before 13 weeks gestation. They found a modest reduction in HbA1c of 2 mmol/mol (0.19%~~0~~ in the CGM~~egm~~ group at 34 weeks, with less time spent in hyperglycaemia, similar to our findings in GDM. Moreover, they were able to demonstrate improvements in the neonatal outcomes of LGA, hypoglycaemia and ICU stay. Yu et al evaluated therapeutic, retrospective CGM in 336 women with GDM (~20% of whom required insulin by trial. ~~-~~end)[19] This Chinese trial compared glycaemia in both arms with 72-hr CGM assessment at 2 time-points, at the first and 5th week of the trial, but only used sensor-data in the intervention-arm to make management decisions. The trial compared supplementary therapeutic, retrospective 72-hour CGM use at 2-4 week regular intervals with CBG 7 times daily alone (from recruitment at ~26-weeks gestation until delivery) and found significantly lower

glycaemic variability, shorter periods of hyperglycaemia and hypoglycaemia (<3.3 mmol/l) in the intervention arm after 5 weeks of CGM use. These differences in glycaemia as evaluated by CGM parameters were associated with lower infant birth-weight, macrosomia and LGA rate and a composite neonatal outcome rate in the CGM-intervention-arm.[19]. However, the effect of CGM on change in HbA1c by end-of-pregnancy was not reported..

The role of HbA1c in monitoring glycaemia in GDM is not well-established. Current NICE guidelines recommend its' use to assess risk, only in mothers with pre-gestational diabetes [21]. The reliability of HbA1c in pregnancy has been questioned due to confounding factors such as dilutional -anemia and shortened erythrocyte -lifespan [22]. ~~However a strong association was found between HbA1c and average glucose values in pregnancy, thus validating its use to represent average glucose values in pregnancy [23].~~ Recent post hoc analysis of two trials of CGM in pre-gestational diabetes has validated HbA1c as a measure of average glycaemia, albeit with a smaller estimated average blood glucose of 0.67 mmol/L per 11 mmol/mol (1.0%), compared to 1.0 – 2.0 mmol/L per 11 mmol/mol (1.0%) in stable non pregnant people with type 1 and 2 diabetes [23]. Several key papers have linked higher HbA1c in GDM, in both 2nd and 3rd trimester with greater likelihood of macrosomia and adverse perinatal outcomes. Lowe et al found that HbA1c at 24-32 weeks gestation in GDM (after adjustments for age, BMI etc.) was independently predictive of macrosomia, with an odds-ratio of 1.93 in women with an HbA1c >40mmol/mol (5.8%), when compared with an HbA1c <26mmol/mol (4.5%) [24]. Another study showed that women with GDM with HbA1c >34mmol/mol (5.3%), either at diagnosis or pre-delivery, experienced more pregnancy-related adverse events [25]. Despite our small sample population that was powered to demonstrate significant differences in glycemic outcomes but not materno-fetal outcomes, -birth-weight and LSCS-rates were non-significantly lower in the CGM-intervention-group.

Extrapolating from the HAPO (Hyperglycaemia and Adverse Pregnancy Outcomes) study results, we can postulate that the lower mean HbA1c of <33mmol/mol (5.2%) in our CGM women, could have resulted in lower macrosomia rates and perinatal complication rates with a larger sample size [24,25]. Both our study arms achieved CBG similar to the landmark GDM trial by Landon et al [4]. HbA1c however is a better integrated measure of glycaemia than CBG profiles or the periodic CGM utilized by Yu et al. Although HbA1c reflects average glycaemia over 8-12 weeks, and therefore the outcome measure we used may have included the glycaemic period before enrolment at 28 weeks, it is well established that the last 30 days of glycaemia has the greatest impact on glycation [26] -Therefore, the progressively increasing HbA1c in late pregnancy as seen in our standard care women, may imply deteriorating glycaemic control in late-pregnancy a~~nd~~s has been seen in other studies [14,15,20]. In addition, as our primary outcome was change in HbA1c from 28-37 weeks, this reduces the possibility that the significant difference in delta A1c between the groups could be substantially affected by pharmacotherapy or lifestyle modification prior to enrolment at 28 weeks, despite the fact that a -proportion of patients had GDM diagnosed before 20 weeks gestation. Additionally, baseline HbA1c at enrolment (28 weeks gestation) was not significantly different between the two arms thus making it likely that any change in HbA1c subsequently was secondary to the CGM intervention.

There is little consensus on how to define 'hypoglycaemia' in pregnancy, with few studies reporting hypoglycaemia rates in insulin-treated women with GDM. The biochemical hypoglycaemia threshold of 4.0mmol/L in our trial was chosen as it is similar to that used in management of non-gravid women with type 1 and 2 diabetes on pharmacological treatment [27]. While NICE 2015 guidelines recommend keeping blood glucose above 4.0mmol/L in insulin-

treated diabetes in pregnancy [21], there is no guidance from the American Diabetes Association (ADA) on lower limits of desirable blood-glucose in GDM [28].

We found a higher incidence of hypoglycaemia in CGM-mothers compared with standard care, especially in the last 4 weeks of the trial. 94.8% of hypoglycaemia episodes with concomitant CBG had readings in the range of 3-4mmol/L. However as interstitial glucose levels are known to drop as low as 2.8mmol/L in healthy pregnancies[29,30] and previous studies have used cut-offs as low as 2.7mmol/L to diagnose hypoglycaemia in pregnancy[7,31], it is difficult to ascertain if these mainly asymptomatic reduced glucose readings are of clinical significance. In contrast, symptomatic hypoglycaemia, which may have more clinical relevance in pregnancy, was similar between groups. None of the participants had severe hypoglycaemia. Importantly, CGM parameters available only in the intervention group demonstrate improvement in glycaemia with no increased time in hypoglycaemia indicating that women were not more hypoglycaemic as a result of better glycaemic control. The improvement in time in euglycaemia can be explained by reduction in time in hyperglycaemia. Of note, there were no SGA babies in either arm and gestational weight gain in both groups were similar and as per IOM recommendations [32], indicating that improved glycaemic control in the intervention arm was not at the expense of reduced caloric intake. We used CBG to enable valid comparisons of hypoglycaemia outcomes between groups as this was utilized by both. This is a limitation of our study design, as it is possible standard care might have had episodes of low glucose missed by CBG. Yu et al, on the other hand, used CGM in both groups, finding that time spent in hypoglycaemia was >5-fold higher in standard care compared to the intervention arm [19]. However, CGM is less reliable when it comes to the lower range of glucose values [33].

To our knowledge, this is the first prospective, randomized controlled trial of therapeutic CGM use exclusively in insulin treated GDM, focusing on HbA1c and hypoglycaemia. Efforts were made to ensure both treatment-arms received equal care in terms of follow-up, dietary and diabetes nurse-educator advice, and optimization of insulin based on the glycaemic profiles available. We were limited both by a small sample-size, and, as a single-centre study where both participant/clinical practitioner were un~~not~~ blinded perhaps introducing bias. Many of our women were diagnosed with GDM at an early~~ier~~ gestation (<24 weeks), having been screened early, as our centre practices opportunistic universal screening during the 1st encounter with the obstetrician. Although none had a prior history of diabetes, this might indicate a proportion had undiagnosed pre-gestational glucose_ ~~-~~intolerance ~~first presenting in pregnancy~~. Diagnosis of GDM was significantly earlier in the CGM_ ~~-~~group and consequently there was a longer duration of medical-nutrition/pharmacological therapy in the intervention arm, hence raising the possibility that these differences might have contributed to improved glycaemic control in the CGM arm. While we did not collect data on actual frequency of CBG monitoring, it is theoretically possible that the CGM arm had potentially more CBG as they were required to monitor levels at least 4 times a day during each of the three six-day CGM periods. The CGM mothers also had slightly more frequent physician contact (mandatory on insertion/removal of CGM sensors). These factors could also have contributed to improved glycaemic outcomes in the intervention arm. Our findings may not be generalizable to a setting where clinical guidelines mandate more frequent CBG such as 7 points/day as recommended by NICE [21].

In conclusion, we found that therapeutic CGM use just 3 times in the 3rd trimester in insulin-treated GDM and its associated intensive care, safely and effectively lowers HbA1c to a greater extent than standard antenatal care with CBG monitoring alone, without any increase in severe

hypoglycaemia, Our findings suggest that CGM is a useful and safe tool in the management of insulin-treated women with GDM.

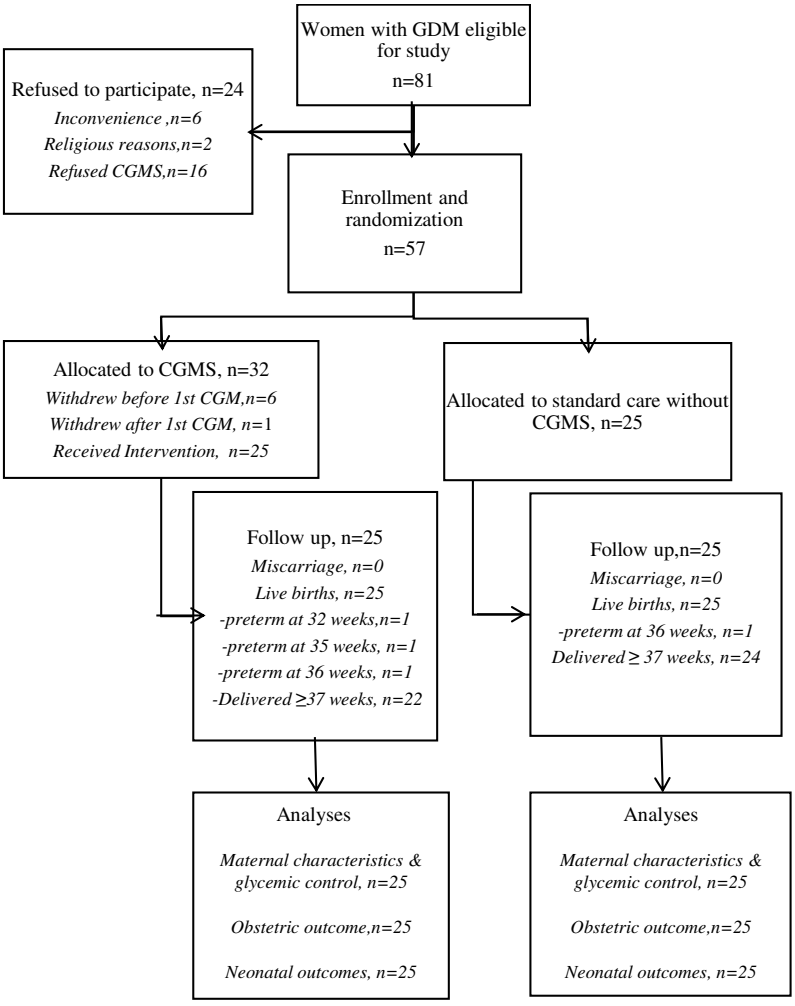

FIGURE 1: Subject distribution and progression through trial

Inclusion Criteria:

- Gestation less than 28-weeks
- Singleton pregnancy
- Confirmed GDM(75g oral glucose tolerance test: fasting plasma glucose ≥5.1mmol/L and/or 2-hour glucose ≥ 7.8mmol/L)(based on local guidelines)[1]
- GDM on insulin-therapy.

Exclusion Criteria:

- Pre-gestational T1DM/T2DM
- Newly diagnosed overt-diabetes in pregnancy.[(HbA1c≥48mmol/mol(6.5%), fasting glucose ≥ 7.0mmol/l, random glucose ≥ 11.1mmol/l)
- Pregnancies with established fetal-anomalies or possible preterm-delivery secondary to maternal-disease besides GDM.
- Known endogenous/exogenous Cushing's-syndrome
- Known chronic infections

Definitions

- Maternal Hypoglycaemia: symptoms or asymptomatic biochemical hypoglycaemia(finger-stick-fasting glucose < 3.5mmol/L and non-fasting glucose < 4.0mmol/L)
- Euglycaemia on CGM: glucose levels 3.5 – 6.7mmol/l

- Large for gestational age: birth weight >90th centile for gestation using Fenton 2013 growth charts[2]
- Small for gestational age: birth weight below the 10th centile using Fenton 2013 growth charts[2]
- Macrosomia: birth weight $\geq$ 4 kg.
- Birth weight ratio(BW adjusted for gestation and gender calculated with the Fenton 2013 web-calculator(http://peditools.org/fenton2013)
- Neonatal hypoglycemia
- <4 hrs of life : <1.4 mmol/L 30 min after 1st feed; <2.2 mmol/L 1hr after subsequent feeds[3]
- 4-24 hrs of life : <1.9 mmol/L prefeed, <2.5 mmol/L 1 hr after feed[3]

[1]Opportunistic universal screening with 75 g OGTT in the fasting state. If an early screen is negative patients are re-screened at 24-28 weeks gestation.

[2]www.ucalgary.ca/fenton

[3]Adamkin DH et al. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127(3);575-579.

TABLE 1: Inclusion Criteria, Exclusion Criteria and Definitions

	CGMS, n=25	Control, n=25	p-value
Age, years [a]	32.8±4.5	32.6±4.9	0.882
Race [b]			
Malay	14 (56.0)	14 (56.0)	0.577
Chinese	5 (20.0)	2 (8.0)	
Indian	5 (20.0)	8 (32.0)	
Others	1 (4.0)	1 (4.0)	
Parity[b]			
Primiparous	13 (52.0)	7 (28.0)	0.083
Multiparous	12 (48.0)	18 (72.0)	
Family history of DM[b]	18 (72.0)	20 (80.0)	0.508
BMI ,kg/m^2 [a]			
Pre-gravid	28.3±4.8	27.3±5.6	0.481
28 weeks	31.4±5.3	30.3±5.4	0.475
Gestational age at diagnosis,weeks[a]	18.8±3.7	20.7±2.7	0.041
HbA1c (28 weeks),mmol/mol(%)[a]	32±3(5.1±0.3)	34±6(5.3±0.5)	0.124
Fasting blood glucose mmol/L (28 weeks)[a]	4.4±0.7	4.3±0.5	0.646

Metformin therapy, from initiation to enrolment(28 weeks):			
No. of women on metformin [b]	8 (32)	11 (44)	0.382
Duration of metformin ,weeks [a]	4.6±3.6	4.8±3.4	0.901
Insulin therapy, from initiation to enrolment(28 weeks) :			
Duration of insulin therapy,weeks [a]	5.0±3.1	4.9±3.0	0.926
Total insulin dose on initiation,units [a]	14.0±8.2	14.0±8.2	0.923
Gestation of insulin initiation,weeks [a]	23.0±2.9	23.0±2.9	0.320
Intensification of insulin from initiation to enrolment (28 weeks) :			
Change in total daily dose,units [a]	3.2±8.8	4.8±8.0	0.482
No. of women with increased no. of injections, [b]	2 (8)	3 (12)	0.193
Insulin dose at enrolment (28weeks),units[a]			
Total	28.0±16.0	28.3±15.9	0.937
Basal	8.3 ±6.5	10.0±5.3	0.323
Bolus	19.6±13.1	18.4±12.6	0.734
Frequency of Health-care provider contact before enrolment(28 weeks) [c] :			
Physician/diabetologist	2(1.5-4),[0-9]	3(1.5-3.5),[0-8]	0.992
Diabetes nurse educator	0,[0-2]	0,[0-1]	0.540
Dietician	2(1-2),[1-4]	2(1-3),[1-6]	0.226

[a] Data expressed as mean±SD [b] Data expressed as n (%) [c] Data expressed as median no. of visits

TABLE 2: Baseline characteristics of women with insulin-treated GDM in CGM and control group

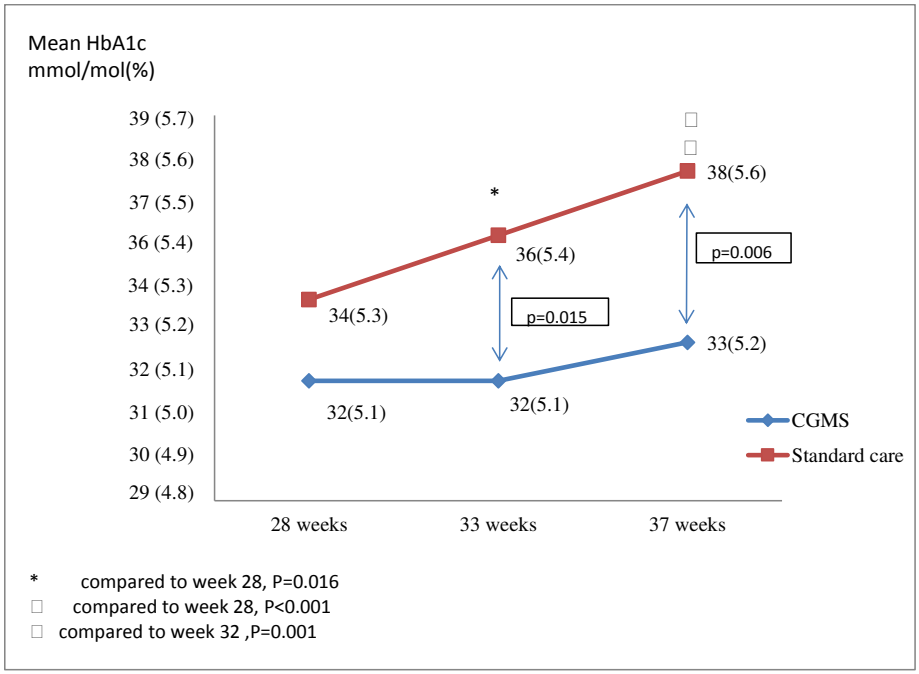

FIGURE 2: Mean HbA1c at 28,33 and 37 weeks in CGM and standard care group

		CGMS	CONTROL	P VALUE
HbA1c, mmol/mol(%)				
Week 28		32±3(5.1±0.3)	34±6(5.3±0.5)	0.124
Week 33		32±4(5.1±0.4)	36±7(5.4±0.6)	0.015
Week 37		33±4(5.2±0.4)	38±7(5.6±0.6)	0.006
Fasting Plasma Glucose at 37 weeks, mmol/L[a]		4.1±0.7	4.6±0.9	0.101
CSMBG, mmol/L[a,b]				
Week 28	Fasting	4.9±0.4	4.8±0.4	0.299
	Pre-meals	5.3±0.4	5.2±0.4	0.249
	2-hours Post-meals	6.0±0.5	5.9±0.4	0.688
Week 32	Fasting	4.8±0.4	4.7±0.4	0.237
	Pre-meals	5.2±0.4	5.0±0.5	0.064
	2-hours Post-meals	6.0±0.5	5.8±0.4	0.191
Week 36	Fasting	4.6±0.4	4.7±0.4	0.400
	Pre-meals	5.2±0.5	5.1±0.4	0.615
	2-hours Post-meals	5.9±0.5	5.8±0.4	0.500

[a] Data as expressed as means ± SD

[b] CBG readings were obtained from a one week record at 3 time-points(week 28, 32 and 36)and an average value of the weekly readings were used for analysis. Pre-meal readings included pre-lunch, pre-dinner and pre-bed CBG. 2-hours post-meal readings included 2-hour post breakfast, lunch and dinner CBG.

TABLE 3: HbA1c, fFasting blood glucosesugar and capillary blood glucoseFingerstick glucose in CGM and standard-care groups

HYPOGLYCAEMIA	CGM	CONTROL	P Value
***Symptomatic, and asymptomatic [finger-stick glucose, fasting<3.5,nonfasting <4.0mmol/L]**			
Whole Study duration [a] (28 -37 weeks)	8.0 (3-14), [1, 34]	4.0 (1-6.5), [1, 12]	0.024
Last 4 weeks[b] (34-37 weeks)	4.0 (3-9), [1, 16]	2.0 (1-3.25), [1, 4]	0.008
Symptomatic (With or without capillary blood glucose~~finger-stick glucose~~)			
Whole Study duration[a] (28-37 weeks)	3.0 (1-6), [0,29]	1.0 (1-4), [0,10]	0.192
Last 4 weeks (34-37 weeks)[b]	3.0 (0-4.5), [0,11]	1.0 (0-2), [0, 2]	0.091

[a]Data expressed as median no. of events per women for whole study duration

[b]Data expressed as median no. of events per women for 4 weeks

TABLE 4: Hypoglycaemia rates in CGM and standard -care groups

	CGM	CONTROL	P VALUE
Total insulin dose, units [a]			
28 weeks	28.0±16.0	28.3±15.9	0.937
33 weeks	38.8±21.4	35.1±20.2	0.539
37 weeks	44.1±25.5	40.1±23.2	0.568
Intensification of insulin from enrolment (28 weeks) till 37weeks:			
Change in total daily dose, units [a]	16.1±16.4	11.8±13.6	0.314
No. of women with increased no. of injections, [b]	6 (26)	5 (22)	
No. of women on intensive insulin therapy at 37 weeks (≥ 4 injections/day)[b]	17 (74)	14 (56)	0.195
No. of women on insulin analogues at 37 weeks [b] (aspart, lispro, levemir)	18 (72)	13 (52)	0.057
No of women on metformin from 28 weeks till 37 weeks [b]	19 (76)	19 (76)	1.000
Frequency of Health-care provider contact from enrolment(28 weeks) till 37 weeks [c] :			
Physician/diabetologist	7(5-8)[3-12]	6(5-8)[0-10]	0.617
Diabetes nurse educator	0[0-1]	0[0-1]	0.317
Dietician	0(0-1)[0-2]	0(0-1)[0-9]	0.956

[a] Data expressed as mean±SD [b] Data expressed as n (%) [c] Data expressed as median no. of visits

TABLE 5: Insulin, metformin therapy and health-care provider contact post-enrolment in CGM and standard-care group

Maternal/Fetal Outcomes	CGM, n=25	CONTROL, n=25	P Value
Maternal Weight gain,kg [a]			
Total	10.1±7.0	10.3±5.0	0.917
From 28 weeks	3.2±2.8	3.0±1.6	0.737
Mean gestation at delivery, week[a]	37.3±1.3	37.7±0.6	0.222
Mode of Delivery[b]			
Vaginal	15 (60.0)	11 (44.0)	0.258
LSCS	10 (40.0)	14 (56.0)	
Emergency	5 (50.0)	9 (64.3)	0.678
Elective	5 (50.0)	5 (35.7)	
Neonatal Mortality[b]	0	0	NA
Neonatal Morbidity			
Preterm Delivery <37 weeks[b]	3(12.0)	1 (4.0)	0.609
Fetal anomaly[b]	0	0	NA
Neonatal hypoglycaemia[b]	1 (4.0)	2 (8.0)	1.000
NICU admission[b]	1 (4.0)	1 (4.0)	1.000
Neonatal jaundice[b]	5 (20.0)	4 (16.0)	1.000

Mean Birth weight(grams)[a]	2842.4±448.6	2976.0±473.5	0.311
Birth weight ratio[a,c]	0.9±0.1	1.0±0.1	0.560
Median birth weight centile[a]	20.6±21.9	28±27.3	0.297
Macrosomia (BW>4kg)[b]	0	0	NA
Large for gestational age (>90th centile)[b]	0 (0)	2 (8.0)	0.490
Small for gestational age (<10th centile)[b]	0	0	NA

[a] Data expressed as mean±SD

[b] Data expressed as n (%)

[c]BW adjusted for gestation and gender calculated with the Fenton 2013 web-calculator (http://peditools.org/fenton2013)

TABLE 6: Maternal and fetal outcomes in CGM and standard-care groups

Parameters[a]	CGMS 1, n=23	CGMS 3, n=23	p-value
Time Spent in Euglycaemia(%)[b]	84.6±9.4	88.8±7.0	0.016
Time spent in Hypoglycaemia (%)[c]	2.7±5.0	2.9±3.2	0.812
Time spent in Hyperglycaemia (%)[c]	12.7±9.9	8.3±6.3	0.017
Total Area under the curve	53230.9±19106.1	54509.0±17042.5	0.910
Mean 24 Hour Glucose(mmol/L)	5.4±0.5	5.2±0.3	0.077
Mean Day Time Glucose(mmol/L)	5.5±0.5	5.3±0.4	0.073
Mean Nocturnal Glucose (mmol/L)	5.1±0.1	4.9±0.5	0.180
AUC Above Limit(>6.7mmol/L)	0.1±0.1	0.06±0.07	0.044
AUC Below Limit(<3.5mmol/L)	0.01±0.02	0.01±0.01	0.827

[a] Data expressed as mean±SD

[b] Time spent in euglycemia on CGM: glucose levels 3.5-6.7mmol/L

[c] Time spent in hypoglycemia on CGM: glucose levels <3.5mmol/L

[c] Time spent in hyperglycemia on CGM: glucose levels >6.7mmol/L

TABLE 7**:** Continuous Glucose Monitoring Parameters in the intervention group

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