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ORIGINAL ARTICLE

Feasibility of Closed-Loop Insulin Delivery with a Pregnancy-Specific Zone Model Predictive Control Algorithm

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Abstract

Objective: Evaluating the feasibility of closed-loop insulin delivery with a zone model predictive control (zone-MPC) algorithm designed for pregnancy complicated by type 1 diabetes (T1D).

Research Design and Methods: Pregnant women with T1D from 14 to 32 weeks gestation already using continuous glucose monitor (CGM) augmented pump therapy were enrolled in a 2-day multicenter supervised outpatient study evaluating pregnancy-specific zone-MPC based closed-loop control (CLC) with the interoperable artificial pancreas system (iAPS) running on an unlocked smartphone. Meals and activities were unrestricted. The primary outcome was the CGM percentage of time between 63 and 140 mg/dL compared with participants' 1-week run-in period. Early (2-h) postprandial glucose control was also evaluated.

Results: Eleven participants completed the study (age: 30.6 ± 4.1 years; gestational age: 20.7 ± 3.5 weeks; weight: 76.5 ± 15.3 kg; hemoglobin A1c: $5.6\% \pm 0.5\%$ at enrollment). No serious adverse events occurred. Compared with the 1-week run-in, there was an increased percentage of time in 63–140 mg/dL during supervised CLC (CLC: 81.5%, run-in: 64%, $P=0.007$) with less time >140 mg/dL (CLC: 16.5%, run-in: 30.8%, $P=0.029$) and time <63 mg/dL (CLC: 2.0%, run-in: 5.2%, $P=0.039$). There was also less time <54 mg/dL (CLC: 0.7%, run-in: 1.6%, $P=0.030$) and >180 mg/dL (CLC: 4.9%, run-in: 13.1%, $P=0.032$). Overnight glucose control was comparable, except for less time >250 mg/dL (CLC: 0%, run-in: 3.9%, $P=0.030$) and lower glucose standard deviation (CLC: 23.8 mg/dL, run-in: 42.8 mg/dL, $P=0.007$) during CLC.

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Conclusion: In this pilot study, use of the pregnancy-specific zone-MPC was feasible in pregnant women with T1D. Although the duration of our study was short and the number of participants was small, our findings add to the limited data available on the use of CLC systems during pregnancy (NCT04492566).

Keywords: Artificial pancreas, Closed loop control, Glucose control, Outpatient, Pregnancy, Type 1 diabetes.

Introduction

IT IS WELL known that pregnancy in women with type 1 diabetes (T1D) can be associated with significant maternal and fetal morbidity and mortality. Maternal hyperglycemia has been linked to preeclampsia, medically indicated preterm delivery, labor abnormalities, need for cesarean delivery, and maternal birth trauma.^{1–4} Fetal and neonatal morbidity includes increased risk of congenital malformations, growth abnormalities (fetal growth restriction, small, or large for gestational age fetus or neonate), fluid abnormalities (oligo- and poly-hydramnios), stillbirth, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia, and neonatal intensive care admission.^{5–7} Pregestational and gestational elevated hemoglobin A1c (HbA1c), reduced time in target range, time in hyperglycemia, and episodes of severe maternal hypoglycemia have been associated with poorer outcomes.^{8–11} In addition to the importance of achieving HbA1c goals and glucose targets, maternal glycemic variability has been shown to be associated with adverse fetal outcomes.¹²

Optimal glycemic goals during pregnancy are still debated with respect to specific HbA1c and self-monitored blood glucose (SMBG) targets, despite the evidence supporting the relationship between glycemic control and pregnancy outcomes. Clinical guidelines note that the risk of hypoglycemia needs to be carefully balanced with the risk of hyperglycemia both for the mother and developing fetus.^{13,14} The CONCEPTT trial revealed the benefits of continuous glucose monitoring (CGM) use during pregnancy.⁹ In 2019, the ADA published consensus guidelines for the use of CGM recommending that glycemic targets for pregnant women with T1D should be guided by a time in range (TIR) goal of >70% based on the glycemic target range of 63–140 mg/dL.¹⁵ Despite increased adoption of CGM¹⁶ and the use of more rapid insulin analogs¹⁷ to assist in glycemic management, many pregnant women still struggle to achieve TIR targets¹⁸ and reduce glycemic variability to optimize pregnancy outcomes. Questions remain regarding the benefits for and optimal management of women using sensor-augmented insulin pump therapy (SAP) during pregnancy,¹⁹ as well as the optimal ways to achieve the very narrow maternal glycemic goals and attain optimal maternal and fetal outcomes while minimizing hypoglycemia.

Limited data are available on closed-loop control (CLC) use in pregnancy.^{20–23} The two largest studies currently available from Stewart et al. reported results for 16 women using CLC compared with SAP.^{21,22} The CamAP System (CamDiab Ltd.) is a closed-loop system that bears CE mark for use in pregnant women with T1D. In the United States, there is currently no approved system for patient use during pregnancy outside of a research setting.

To address the unmet needs of pregnant women with T1D in the United States, we designed a zone model predictive

control (zone-MPC) based CLC system specifically customized for use during pregnancy. The zone-MPC runs on the interoperable artificial pancreas system (iAPS),²⁴ which consists of a CGM, an insulin pump, and an unlocked smartphone. Zone-MPC integrated in iAPS has been proven to be safe and effective for glycemic control in previous clinical trials.^{25,26} In this study, we report the first clinical trial results of the feasibility of a pregnancy-specific design of this system evaluated under supervised conditions.

Research Design and Methods

Trial conduct and oversight

This study (NCT04492566) was conducted in pregnant women with preexisting T1D at the Icahn School of Medicine at Mount Sinai (New York, NY), Mayo Clinic (Rochester, MN), and Sansum Diabetes Research Institute (Santa Barbara, CA) after approval by the Mayo Foundation IRB. Written informed consent was obtained from all participants. One REDCap electronic data capture tool (Mayo Clinic) was used to collect and manage the data from all sites.^{27,28}

Participants and trial design

The eligibility criteria for participation included age ≥ 18 and ≤ 45 years, current use of an insulin pump, HbA1c $\leq 9\%$, 14^{0/7} to 32^{6/7} weeks gestation, singleton pregnancy without any other significant known pregnancy complications, and willingness to use bolus insulin for all meals and snacks containing ≥ 5 g of carbohydrate other than when treating hypoglycemia, use insulin aspart (Novolog) or insulin lispro (Humalog) for the CLC session, not to start any new noninsulin glucose-lowering agent during the trial, and to use study-provided devices and to abide by the study protocol. A complete list of eligibility criteria is given in the Supplementary Data.

The study consisted of up to 2 weeks run-in with participants using the study CGM, Dexcom G6 (Dexcom, Inc., San Diego, CA), and personal insulin pump therapy at home, followed by a 2-day supervised CLC period. All participants were provided and trained on the use of the CGM at the start of the run-in to reinforce proper use. The CGM was worn either on the abdomen, posterior upper arm, or buttock based on body habitus, skin findings, and participant preference. During this period, women were instructed to perform daily activities, food consumption and meal boluses as usual. Study clinicians could adjust the participants' treatment parameters (i.e., basal rates, carbohydrate ratios, insulin sensitivity factors) as needed to optimize pump settings based on sensor and pump data reviews before entering the CLC phase. At the end of this run-in period, data were downloaded before the initiation of the CLC study. Insulin pump settings were adjusted based on clinical judgment to address needs per gestational age during or at the end of the run-in phase. No adjustments were made during the CLC session unless otherwise stated.

During the CLC session, participants continued using the study CGM but switched to a research insulin pump (Tandem Diabetes Care, San Diego, CA). The devices connected wirelessly to the iAPS installed on an unlocked study phone (Google Pixel 2 or 3a).²⁴ Participants were supervised by onsite study staff clinically trained in treating hypoglycemia and hyperglycemic emergencies per the clinical study protocol. Before initiating CLC and upon study completion, all enrolled participants at or beyond 23 weeks of gestational age had fetal heart rate recorded by a handheld fetal Doppler (CareFusion, Middleton, WI). Vital signs were recorded on admission and every 12 h.

Participants chose their meals without nutritional restrictions from nearby restaurants or markets and ate all meals at the supervised site. SMBG testing was performed before and 2 h after each meal. Hypoglycemia treatments occurred when either SMBG was <63 mg/dL or if participant wished to treat a glucose level above the 63 mg/dL threshold. For glucose levels <63 mg/dL, a repeat SMBG measurement was performed every 15 min after the rescue carbohydrate consumption until the hypoglycemic event was resolved. Additional testing was performed at bedtime. Participants were permitted to snack at any time, administer meal boluses per their home routine as well as exercise as per their typical routine and ingest additional carbohydrates for exercise, if needed.

Reportable events were categorized as those leading to hospitalization, occurring in association with a study device, severe hypoglycemia (defined as hypoglycemia requiring assistance owing to altered consciousness), diabetic ketoacidosis as defined by the Diabetes Control and Complications Trial, or hyperglycemia with ketonemia leading to injury or hospitalization.²⁹ Owing to the more stringent glucose targets during pregnancy, moderate hyperglycemic events are reported for circumstances where the sensor glucose level was >180 mg/dL for more than 60 min without a dietary explanation.

Closed-loop system

The zone-MPC algorithm solves an optimization problem that minimizes the predicted glucose values' deviations from a time-dependent target zone.³⁰ The cost for the glucose deviations above the zone are weighted by predicted glucose velocity and insulin on board (IOB) for enhanced hyperglycemia response as well as for limiting controller-induced hypoglycemia. The predicted glucose velocity is also used for assertive response to rapidly upward trending glucose. Finally, asymmetric costs for controller-delivered insulin deviating below and above the prescribed basal rate are induced to independently address hypoglycemia and hyperglycemia, respectively. The optimal insulin delivery plan is updated every 5 min based on new CGM data. Thus, the controller-delivered insulin can be highly time varying, in contrast to the preprogrammed basal rate, which is held constant for the specific times of the day. The optimization is subject to insulin-glucose dynamics and time-dependent insulin delivery and IOB constraints to prevent insulin stacking.

The *pregnancy-specific zone-MPC* was designed to address the tighter glucose control requirements in pregnancy. The target zones were redesigned to 80–110 mg/dL during the day and 80–100 mg/dL during the night from 12 to 4 AM,

which are lower than the values used for the nonpregnant T1D population. Insulin delivery was more assertive when the blood glucose values were trending upwards while in 120–180 mg/dL range. Furthermore, postprandial control was intensified by relaxing the controller's IOB constraint. Details of these changes are provided elsewhere³¹ and summarized in Supplementary Data.

Meals were announced to the system by the user, and meal boluses were calculated based on the participants' prescribed bolus settings (i.e., carbohydrate ratio and insulin sensitivity factor) and user-estimated carbohydrate intake. Changes to meal bolus calculations were as follows: (1) full meal bolus was applied when blood glucose values were >70 mg/dL; (2) a correction was automatically added to the bolus to bring the glucose to reference glucose of 90 mg/dL if premeal glucose was >100 mg/dL; and (3) meal boluses were automatically reduced by 20% when mealtime glucose was <70 mg/dL. Note that the total insulin delivered during the CLC is the sum of controller-delivered insulin and user-requested bolus insulin.

A safety layer, Health Monitoring System, independent of the control algorithm, was embedded in the iAPS for improved safety against hypoglycemia through audiovisual advisory alarms and text messages.³² The system was set to produce an alert on the phone screen when it predicted a glucose value <65 mg/dL within the next 15 min. As the CLC system is an insulin-only system, hypoglycemia treatments were at the users' discretion. Users could also choose to administer additional correction boluses through the system.

Study endpoints

The primary endpoint was the percentage of time that CGM glucose level was in the 63–140 mg/dL target range. Secondary outcomes were the overnight percentage of time in the target range, 2-h postprandial percentage of time in the target range, percentage of time below thresholds of 63 and 54 mg/dL, and percentage of time >140, 180, and 250 mg/dL.^{14,15} Additional secondary outcomes were mean CGM glucose, glycemic variability assessed by both glucose standard deviation (SD) and coefficient of variation, the number of treatments for hypoglycemia, serious adverse events, serious adverse device events, adverse device effects, and unanticipated adverse device effects during the 2-day supervised study session. A root cause analysis of the event was performed to determine if the event was related to a component of the CLC system. Other outcome measures included active time in closed-loop, CGM use time, device issues, and total daily insulin delivery along with basal and bolus insulin delivery.

Statistical analysis

Statistical analyses were conducted on data from all participants. Glycemic outcomes were calculated based on the CGM data collected during the last week of run-in period for the home portion compared with the CGM data collected during the supervised study visit for the closed-loop portion. In addition to the overall glucose control measures, we assessed the overnight (midnight–6 AM) outcomes for both parts of the study. Controller-delivered insulin, user-requested insulin (meal and correction boluses), and total insulin during the CLC phase were calculated. The

controller-delivered insulin was compared with the participants' total preprogrammed basal insulin profile over the same period. No comparisons were made for the observed basal, bolus, and total insulin between the run-in and CLC sessions owing to variable day-to-day factors (e.g., carbohydrate intake, physical activity).

Paired *t*-test was used to compare results between run-in versus CLC study periods. Exclusively for the CLC portion, we analyzed postprandial glucose control performance by evaluating the 2-h postprandial CGM readings in accordance with American Diabetes Association guidelines noting the importance of 1 and 2 h postprandial glucose values in this population.¹⁴ The performance was assessed based on the percentage of time in the target range within the first hour [0–1 h] and within the first 2 h [0–2 h] of meal intake. To assess full CGM trajectory of the early postprandial period, only main meals (i.e., breakfast, lunch, and dinner) consumed up to 2 h before the end of the CLC session were included in these analyses. Since there were multiple meals consumed per participant, linear mixed-effects regression models were used to account for the repeated measurements.

Results are presented as mean ± SD for descriptive statistics and paired *t*-test outcomes. Linear mixed-effect regression results are reported as the regression model estimate ± standard error. A two-sided significance level of 0.05 was used in all statistical analyses. There were no adjustments for multiple comparisons. Data processing was performed in MATLAB R2019b (MathWorks, Inc., Natick, MA), and we used R (R Core Team, 2019) for statistical analyses.

Results

Participant characteristics

Between August 2020 and June 2021, 11 participants were enrolled at age 30.6 ± 4.1 years with the following baseline characteristics at enrollment: gestational age of 20.7 ± 3.5 weeks, weight of 76.5 ± 15.3 kg, body mass index of 27.8 ± 4.5 kg/m², and HbA1c of 5.6 ± 0.5% (38 ± 5 mmol/mol). All participants were on SAP before enrollment with a mean (±SD) total daily insulin dose of 51.2 ± 16.2 units. Baseline study participant characteristics are given in Table 1.

Study outcomes

Supervised CLC sessions lasted 47.7 ± 2.5 h, and participants stayed in closed-loop 98.0% ± 1.3% of the time. CLC increased the percentage of time spent in the 63–140 mg/dL range (CLC: 81.5%, run-in: 64%, *P* = 0.007) by decreasing both time >140 mg/dL (CLC: 16.5%, run-in: 30.8%, *P* = 0.029) and time <63 mg/dL (CLC: 2.0%, run-in: 5.2%, *P* = 0.039). Furthermore, CLC improved the outcomes for times <54 mg/dL (CLC: 0.7%, run-in: 1.6%, *P* = 0.030), >180 mg/dL (CLC: 4.9%, run-in: 13.1%, *P* = 0.032), and in the broader glycemic range of 70–180 mg/dL (CLC: 90.1%, run-in: 77.6%, *P* = 0.003). Glycemic variability was less with CLC, as measured by both SD (CLC: 31.2 mg/dL, run-in: 42.6 mg/dL, *P* = 0.017) and coefficient of variation (CLC: 28.0%, run-in: 34.2%, *P* = 0.047). The only differences in overnight glucose control between therapies were time >250 mg/dL (CLC: 0%, run-in: 3.9%, *P* = 0.030) and glucose variability measured by glucose SD (CLC: 23.8 mg/dL, run-in: 42.8 mg/dL, *P* = 0.007). Detailed results and additional

TABLE 1. DEMOGRAPHICS OF STUDY PARTICIPANTS AT ENROLLMENT

Number of participants	11
Age (years)	30.6 ± 4.1
Ethnicity	Not Hispanic or Latino (100%)
Race	White (100%)
Weight (kg)	76.5 ± 15.3
BMI (kg/m ²)	27.8 ± 4.5
HbA1c	5.6% ± 0.5% (38 ± 5 mmol/mol)
Systolic BP (mmHg)	107.9 ± 8.2
Diastolic BP (mmHg)	65.8 ± 7.1
Heart rate (bpm)	86.8 ± 11
Gestational age	20.7 ± 3.5
Gravida	2.0 ± 1.3
Parity	0.8 ± 1.4
Pump-	
Tandem t: slim x2 (Basal IQ)	4
Tandem t: slim x2 (Control IQ)	2
Tandem t: slim x2 (Manual mode)	2
Medtronic 670G (Manual mode)	2
Omnipod Eros	1
Duration of pump use	
<3 months	1
1–5 years	5
5–10 years	1
>10 years	4
CGM user at enrollment	11
Duration of CGM use, years	
1–5	9
5–10	1
>10	1
Average total daily insulin-1 week before 48-h study (Units)	51.2 ± 16.2

BMI, body mass index; CGM, continuous glucose monitor; HbA1c, hemoglobin A1c.

outcomes for both day-and-night and overnight alone are given in Table 2. Figure 1A provides the daily median and interquartile range of CGM measured glucose trajectories across all participants. Individual breakdowns of glycemic outcomes show that 9 of 11 participants had an improved outcome in at least one of the metrics as given in Figure 1B and C. For eight participants, CLC improved TIR, time <63 mg/dL, and time >140 mg/dL altogether.

Participants had three main meals each day of the CLC session with the content and size of meals at their discretion. The meal amount entered into the meal bolus calculator was also decided by the participants. Combined with snacks, total carbohydrate entry over the CLC period was 272.5 ± 109.6 g per participant. Of the 66 meals consumed, 60 were eaten more than 2 h before the CLC session ended and were included in the analyses. For the meals included in the analyses, the carbohydrate content per meal ranged from 10 to 78 g, with an average of 39.6 ± 18.7 g. CGM glucose at mealtime before food ingestions was 98.8 ± 21.1 mg/dL. The average estimated TIR was 86.4% ± 3.9% for the first hour and 80.4% ± 4.9% for the first 2 h of the postprandial window.

Of all hypoglycemia treatments, 58% of them were required within 3 h of a meal bolus, and rescue carbohydrate intake ranged from 3 to 16 g. Episodes requiring additional consumption of carbohydrate were reported as a new event. Ten

TABLE 2. CONTINUOUS GLUCOSE MONITOR METRICS COMPARING THE PERFORMANCE OF THE CLOSED-LOOP PERIOD WITH THE RUN-IN PERIOD

Sensor glucose metrics	Time	Closed-loop session (N=11)	Run-in week (N=11)	P
% Time 63–140 mg/dL	Day and night	81.5 ± 12.3	64.0 ± 17.5	0.007**
	Overnight	75.2 ± 31.8	59.7 ± 19.8	0.167
% Time 70–180 mg/dL	Day and night	90.1 ± 5.6	77.6 ± 10.4	0.003**
	Overnight	88.1 ± 13.7	75.9 ± 12.2	0.083*
% Time <54 mg/dL	Day and night	0.7 ± 1.4	1.6 ± 1.9	0.030**
	Overnight	0.2 ± 0.7	1.4 ± 2.3	0.132
% Time <63 mg/dL	Day and night	2.0 ± 2.5	5.2 ± 6.0	0.039**
	Overnight	0.5 ± 1.5	4.9 ± 7.7	0.105
% Time <70 mg/dL	Day and night	5.0 ± 4.2	9.2 ± 9.5	0.075*
	Overnight	2.2 ± 3.8	8.0 ± 11.0	0.115
% Time >140 mg/dL	Day and night	16.5 ± 12.5	30.8 ± 20.5	0.029**
	Overnight	24.3 ± 31.6	35.4 ± 23.4	0.317
% Time >180 mg/dL	Day and night	4.9 ± 5.1	13.1 ± 12.0	0.032**
	Overnight	9.6 ± 14.1	16.1 ± 13.9	0.346
% Time >250 mg/dL	Day and night	0.3 ± 0.8	2.9 ± 4.2	0.061*
	Overnight	0 ± 0	3.9 ± 5.2	0.030**
Mean glucose (mg/dL)	Day and night	110.2 ± 12.6	124.7 ± 26.6	0.058*
	Overnight	118.8 ± 27.1	131.4 ± 30.8	0.130
SD glucose (mg/dL)	Day and night	31.2 ± 9.1	42.6 ± 11.5	0.017**
	Overnight	23.8 ± 13.1	42.8 ± 14.4	0.007**
CV glucose (%)	Day and night	28.0 ± 6.5	34.2 ± 7.0	0.047**
	Overnight	19.4 ± 8.3	32.4 ± 8.9	0.366

The data are shown as mean ± SD.

*0.05 < P < 0.1.

**P ≤ 0.05.

SD, standard deviation.

participants required treatment for hypoglycemia, and the number of treatments consumed per CLC session per participant ranged from 0 to 13, with an average of 4.7 ± 4.1, as detailed in the Supplementary Data. All treatments were self-administered by the participants.

There was no significant difference between the controller-delivered insulin and the overall programmed basal insulin amounts (CLC: 45.2 ± 19.2 units, basal profile: 48.3 ± 21.3 units over the CLC session, P=0.13). The average user-requested bolus during the CLC was 44.1 ± 20.7 units, and the total insulin delivered was 89.2 ± 37.2 units over the CLC session, averaged across participants. Detailed visuals for each participant's glucose profiles are provided in the Supplementary Data. Figure 2 provides a closer view of two participants' CLC data that are of particular interest as one had the highest TIR and low total carbohydrate intake, whereas the other one had the highest total carbohydrate intake among participants. Both participants achieved a TIR that was approximately twice of their TIR in the run-in week (100% vs. 51.8% in the participant given in Fig. 2A and 67.8% vs. 32.9% in participant given in Fig. 2B).

Safety and adverse events

One device issue occurred leading to a loss of CGM data for 95 min soon after a meal (Participant 6), which required re-entry of device settings on the study phone. The participant reverted to open loop during this time with transient hyperglycemia with a peak SMBG level of 259 mg/dL when reconnection was resumed. The participant administered a correction bolus and hyperglycemia resolved within 2 h of resumption of CLC insulin delivery. One episode of moder-

ate hyperglycemia occurred overnight with the participant receiving intermittent occlusion alerts (Participant 5). SMBG and ketones were checked and were 185 mg/dL and 0.4 mM, respectively. The infusion site was changed at 3:30 AM, and by 4:20 AM CGM values dropped to 174 mg/dL. Another infusion set change occurred owing to irritation/itching at the infusion site with a CGM glucose level of 119 mg/dL. Both participants' overnight basal profiles were increased for the second night. No hospitalizations, episodes of ketoacidosis, or severe hypoglycemia occurred. The participant who consumed 13 hypoglycemic treatments during the study reported a long-standing history of preference for lower glucose levels and did not require assistance for any of her treatments.

Discussion

Our study reports the first CLC outcomes in pregnant women in the United States using a novel zone-MPC design specifically customized to meet the CGM TIR targets for pregnancy based on consensus guidelines.¹⁵ Compared with the 1-week run-in, there was an increased percentage of time in the 63–140 mg/dL range accompanied by decreased percentages above and below this range, during the supervised CLC session. Moreover, 9 of 11 participants had a greater TIR during CLC. Since every additional 5% improvement in maternal TIR during pregnancy can improve pregnancy outcomes,³³ the glycemic control achieved by our CLC system has clinical significance. Equally important, no adverse safety events occurred, and sessions were completed without severe hyperglycemia or severe hypoglycemia despite the stricter glycemic targets. Six of 11 participants were already using an insulin pump with predictive low-glucose suspend

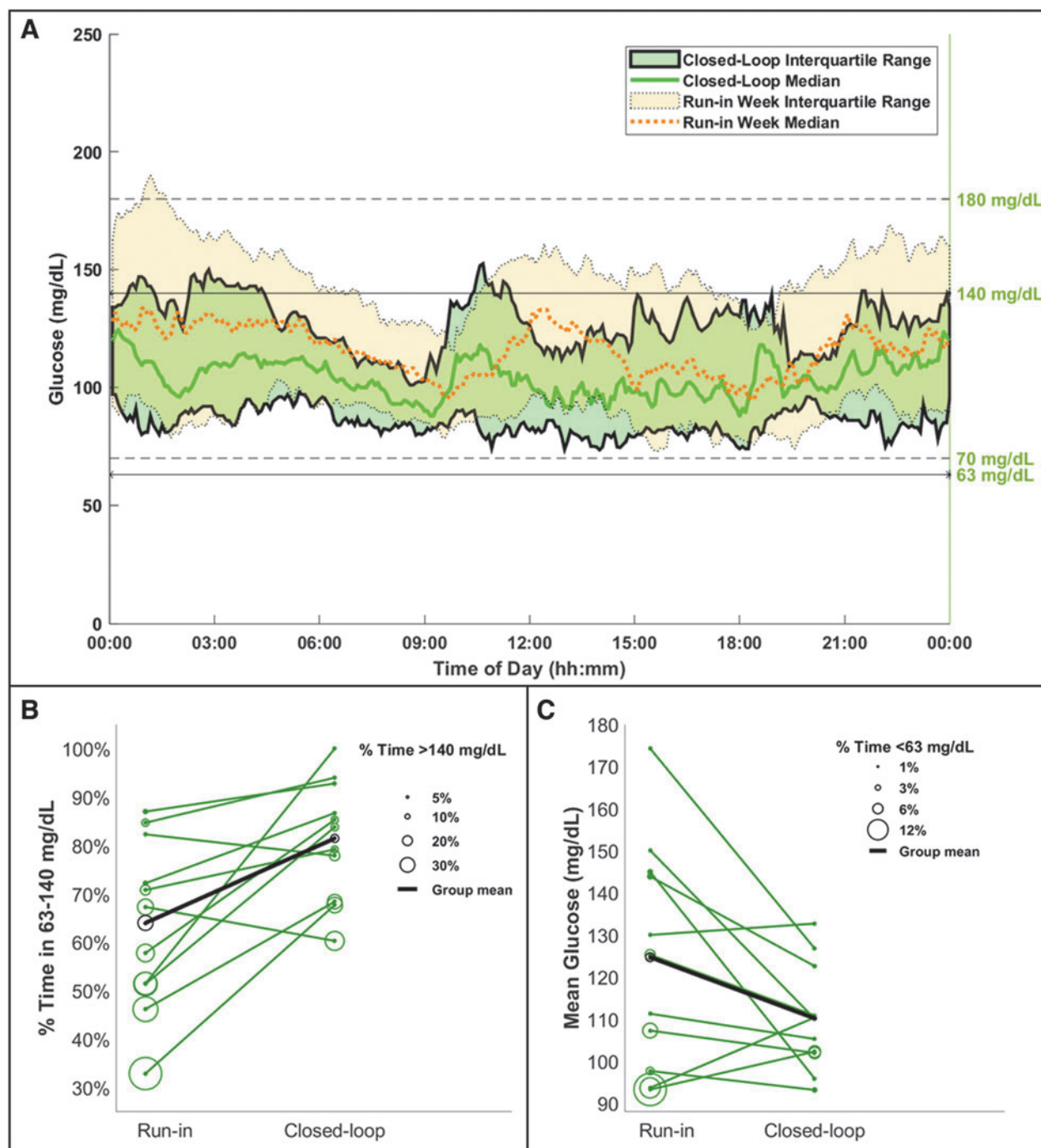


FIG. 1. (A) Comparison of CGM glucose levels between CLC therapy (solid traces and green area) and participants' standard therapy (dashed traces and yellow area), (B) individual breakdown of time spent in the target range on the y-axis and time spent above the target range is represented by circles, (C) individual breakdown of mean CGM glucose on the y-axis and time spent below the target range is represented by circles. CGM, continuous glucose monitor; CLC, closed-loop control.

features (i.e., Tandem Basal-IQ, or Tandem Control-IQ technology) during their run-in week, which had likely already helped decrease episodes of hypoglycemia in the run-in week.

For the early postprandial period, the high percentage in the target glucose range achieved by the *pregnancy-specific zone-MPC* is noteworthy because meal-related glucose control may become particularly challenging in pregnancy with

T1D.³⁴ The high postprandial performance may have resulted in more than half of the hypoglycemia treatments in the CLC session occurring within 3 h of a previous meal bolus. This may be owing to one or a combination of factors, such as inaccurate carbohydrate counting, suboptimal meal bolus parameters, and/or the CLC system's assertiveness level in the postprandial period. Further studies can provide better insight on this matter.

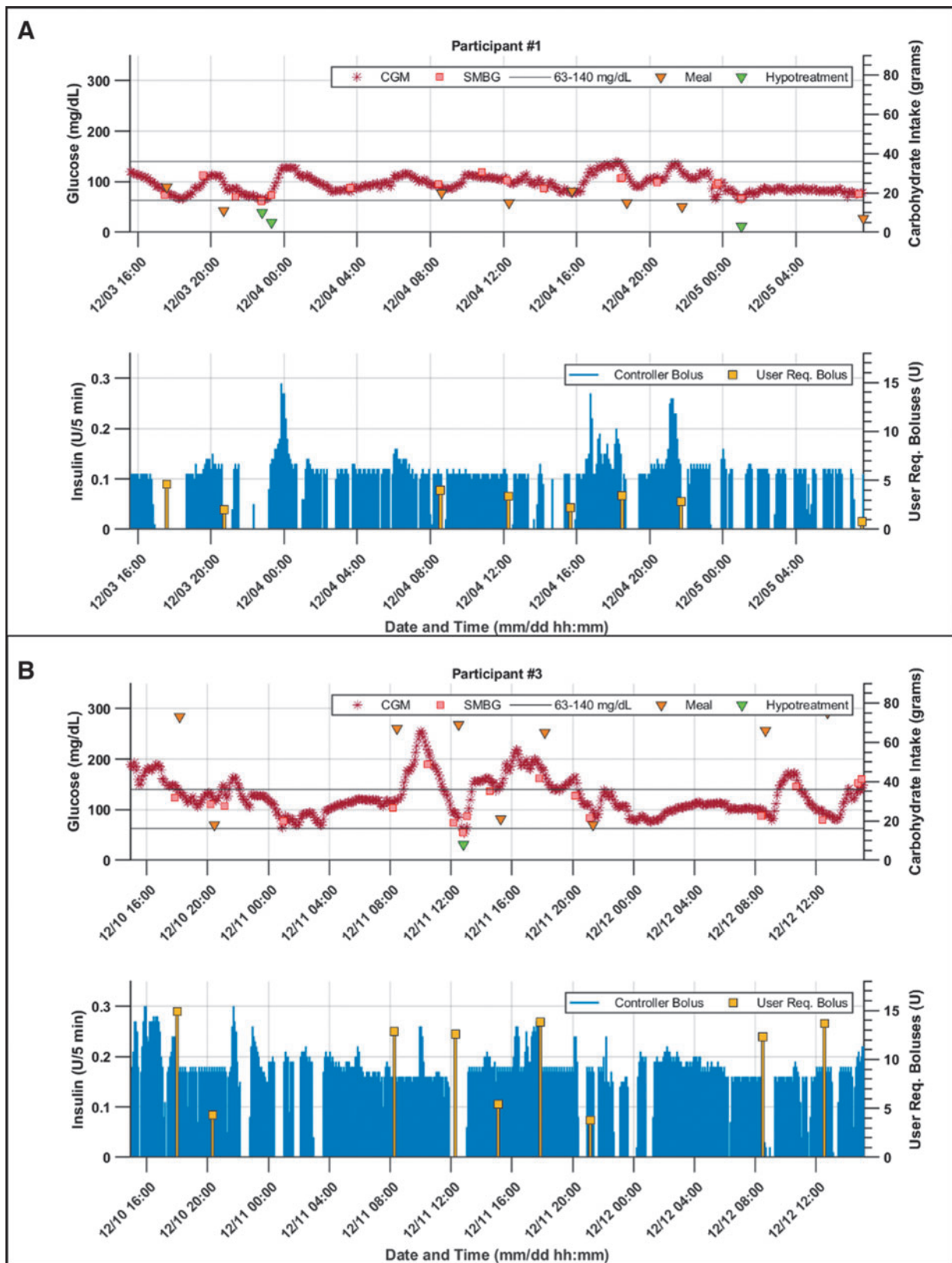


FIG. 2. CLC session glucose, meal, and insulin delivery of (A) the participant with highest CGM time in the target 63–140 mg/dL range (100%) and low carbohydrate intake (125 g), and (B) the participant with highest carbohydrate intake (472 g). For both participants, the top figure shows the glucose on the left axis and carbohydrate intake amounts on the right axis; the bottom figure shows the controller decided micro-bolus deliveries on the left axis and the user requested boluses (i.e., meal and additional correction) are presented on the right axis. Note that participant numbers are assigned arbitrarily.

Previous reports of other CLC systems show a higher overnight performance compared with the day-and-night time performance. This was not the case for our study potentially owing to (1) late dinners—many from restaurants—with higher fat and protein content, without carbohydrate labeling making estimations for meal bolus more challenging, and (2) the conservative lower nighttime upper limit for microboluses (i.e., four times the prescribed basal rate per 5-min intervals) compared with the daytime limit (i.e., 1 unit per 5-min interval) to protect against nocturnal hypoglycemia.

Although the duration of our study was short and the number of participants was small, our findings are important because of the limited data available on the use of CLC systems during pregnancies complicated by T1D in an outpatient setting, and the significant glycemic improvements obtained with the CLC system. Few other CLC studies in an outpatient setting have been conducted in pregnant women with T1D. In an open-label, randomized, crossover study comparing a CLC system with sensor-augmented pump therapy worn overnight, Stewart et al. found that CLC users spent significantly more TIR (74.7% vs. 59.5%) and had lower overnight mean glucose levels (119 vs. 133 mg/dL).²¹

In a separate report comparing day-and-night CLC to sensor-augmented pump therapy among pregnant participants with T1D, the same research group found that the cohorts had comparable TIR (62.3% vs. 60.1%), mean CGM glucose, and proportions of time spent >140 mg/dL.²² A key difference was that the CLC group experienced less hypoglycemia, including less nocturnal hypoglycemia, a finding that can greatly impact the experience of self-care in T1D.²² Of note, compared with these studies, our participants had a lower average HbA1c at enrollment, and some participants were on SAP treatment that involved new advanced technologies (i.e., Tandem Basal-IQ and Control-IQ technologies).

Polsky and Akturk also reported a case series in which they described the experiences of three pregnant women with T1D utilizing off-label Medtronic 670G, the first CLC system to receive the FDA approval.²³ They observed that with increased time spent in automated mode, along with the input of a premeal bolus and “fake carbohydrates,” there was increased time spent in the 70–180 mg/dL range. Our pregnancy-specific zone-MPC also led to a greater time in the 70–180 mg/dL range compared with the participants’ SAP therapy.

Our dataset has limitations because of the small sample size related to COVID-19 pandemic restrictions as well as enrolling a group of women with low HbA1c concentrations (mean 5.6%) mostly in the second trimester of their pregnancy. In addition, this was not a randomized controlled trial, but instead compared a 1-week unsupervised run-in period to a 48 h supervised session. Another potential weakness is that some participants may have been more attentive to their carbohydrate intake, and low glucose levels that required treatment might have been addressed earlier owing to the supervision during the study compared with their normal care. Unlike the CLC period, the alerts placed into the CGM for hypoglycemia during run-in was at the discretion of individuals and may have impacted duration of individual hypoglycemia outcomes between the two sessions. It is important to note that we observed no systematic decrease or increase in the controller-delivered insulin compared with the prescribed basal profiles. Therefore, the consistent

improvement in time below, above, and in the target range was obtained using CLC system-generated proactive timing of insulin delivery, rather than an overall increase in basal insulin use. Our study has strengths owing to its multicenter design, a range of gestational ages, use of various insulin pumps during the run-in, and participants consuming a free range of carbohydrate and meal choices, many of which were higher in fat or carbohydrate content than typically recommended, likely owing, in part, to meal options available during the study.

Conclusions

In conclusion, our pilot study demonstrates that a customized CLC system designed to specifically target glucose goals for pregnancy is feasible for women previously using insulin pumps and CGM. Initial studies enrolling women to assess the use and efficacy of the pregnancy-specific zone-MPC with iAPS in the home setting are currently underway (NCT04492566). Further studies are needed to evaluate this system in a larger group of women and sustained use throughout pregnancy.

LOIS-P Diabetes and Pregnancy Consortium

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Authors’ Contributions

G.O., K.C., Y.C.K., C.J.L., J.E.P., and E.D. were responsible for study design. B.O. designed, tested, and provided primary technical support for the CLC system with supervision of E.D., F.J.D. and assistance from S.D. B.O. conducted the statistical analyses in consultancy with S.D. and W.K.K. B.O., C.J.L. and Y.C.K. led writing the article and all co-authors contributed to the writing. C.J.L., E.D., B.R., J.E.P., and Y.C.K. were principal investigators at their respective sites. S.M.-S. managed the IRB process. C.R. set up the online platform for data access and management. C.L., M.M.C., D.D., M.P., S.O., R.J.K., and S.M.-S. conducted study visits and managed data collection at their sites. CR and BO was responsible for central management of data collection. All authors were responsible for reviewing and revising this article and assume responsibility and accountability for the results. E.D. is the guarantor of this work, and as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Material

Supplementary Data

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