Supplementary materials

Supplement to: At-home use of a pregnancy-specific Zone-MPC closed-loop system for pregnancies complicated by type 1 diabetes: a single arm, observational multicenter study

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Additional Methods

This study was conducted at three clinical sites in the United States between May 2021 to October 2022 and was approved by the United States Food and Drug Administration under an Investigational Device Exemption and the central Institutional Review Board (Mayo Foundation IRB). It is registered at clinicaltrials.gov (NCT04492566). The study device algorithm was developed at the Harvard John A. Paulson School of Engineering of Applied Sciences, Harvard University, Cambridge, MA. Informed consent was obtained prior to all study procedures.

Additional information about devices/system used

The study system consisted of an unlocked Android phone (Google Pixel 3a) containing a pregnancy customized zone-model predictive control algorithm operated by the interoperable Artificial Pancreas System (iAPS), a Tandem t:AP insulin pump (Tandem Diabetes Care), and a Dexcom G6 continuous glucose monitoring (CGM) system. Both the Tandem insulin pump and Dexcom G6 CGM were connected to the study phone via Bluetooth technology. Participants would use the study phone to view their CGM values, enter fingerstick glucose information, bolus for food and corrections, and enter hypoglycemic treatments if needed. There was also a remote monitoring website where study investigators could view the participants' CGM tracing, insulin boluses, hypoglycemic alerts and any hypoglycemic treatments entered. In addition to predictive low glucose alerts, study clinicians would receive real-time alerts for CGM values below 54 mg/dL for > 15 minutes, CGM > 220 mg/dL for 15 minutes, and if the participant had no CGM data for 2 hours or was out of closed loop for 2 hours. It also provides alarms for system malfunction such as loss of connectivity with devices, including text-messages to the study investigators for alarm events such as for impending hypoglycemia and prolonged hyperglycemia and hypoglycemia based on prespecified glucose threshold and time period, per FDA requirements based on the Investigational Device Exemption (IDE) approval.

Eligibility Criteria

Pregnant women were eligible for the study if they met the following criteria: between age 18 and 45 years inclusive, have Type 1 diabetes using an insulin pump, HbA1c ≤ 9% at screening, gestational weeks between $14^{0/7}$ to $32^{6/7}$, singleton pregnancy without any significant known complications such as preeclampsia, premature rupture of membranes, 2nd/3rd trimester bleeding, fetal growth or fluid abnormalities, no proven or suspected fetal malformations diagnosed in the current pregnancy, bolus for all meals and snacks containing ≥ 5 grams of carbohydrate, willing to use aspart or lispro insulins approved for use in the study pump for the duration of closed-loop use, willing to not start any new non-insulin glucose-lowering agents during the trial, willing to abide by the study protocol and use the study-provided devices, and having a care partner living with the participant who is aware of the participant's whereabouts and available for contact by study staff and assisting with emergency care if needed.

Exclusion criteria included having any known unstable or untreated cardiac disease, use of inhaled insulin or any non-insulin glucose-lowering agents other than metformin, any bleeding disorders, prior history of Preterm Premature Rupture of Membranes (PPROM), significant hyperemesis interfering with carbohydrate intake, A1c > 9%, abnormal liver or renal function (transaminase >2 times the upper limit of normal, creatinine > 1.5 mg/dL) within 3 months prior to screening, dermatological conditions that precluded wearing a CGM sensor or infusion site, any condition that could interfere with participating in the trial, participation in another pharmaceutical or device trial at the time of enrollment or during the

study, having a direct supervisor at the place of employment or first-degree relative who is also directly involved in conducting the clinical trial, history of severe hypoglycemia or diabetes ketoacidosis (DKA) requiring hospitalization in the past 6 months, significant chronic kidney disease (eGFR < 60) or hemodialysis, significant liver disease, history of adrenal insufficiency, abnormal TSH consistent with hypo- or hyperthyroidism that was not appropriately treated, or history of high dose steroid use in the past 8 weeks prior to screening.

Additional information about study procedures

Once participants were screened and enrolled, they were trained on how to use the Dexcom G6 system and started a CGM run-in phase for one to two weeks using their personal insulin pump and the study provided Dexcom G6 for data collection. The second phase was a 48-hour closed loop session in a supervised outpatient setting with at least one clinician present at all times, where the participants were free to conduct their usual daily activities. Participants were then given the option of continuing use of the study system at home (the third phase) until the end of pregnancy but before delivery, of which all participants in this study opted to do. These participants were trained on use of the study pump and phone prior to bringing the system home, with a 24-hour, 48-hour and 72-hour check-in by the study team after discharge. Participants were also trained on how and when to use the study blood ketone meter. Once at home with the study system, participants were required to perform at least 7 fingerstick glucose (SMBG) tests a day for the first two weeks using the study glucometer (Contour Next One), and if ≥ 90% of CGM values were within 20%/20 mg/dL of SMBG readings, this requirement would be lifted for the rest of the study. Otherwise, they would continue with the two-week SMBG requirement and reassessed until they met the fingerstick accuracy criteria.

After about 4 weeks of system home use by the first three participants, the Data Safety and Monitoring Board (DSMB) reviewed a summary of the participants' glycemic data (CGM % time ≤ 54 mg/dL = 2% or less, CGM % time 63-140 mg/dL = 50% or greater) and any adverse events and approved continued use of the system throughout the remainder of pregnancy for all participants in the study.

The at-home phase consisted of a follow-up contact once a week by study investigators, involving review of glycemic and insulin data via the remote monitoring website, adverse events, medical condition or medication changes and device issues. Participants were also reminded to keep their home insulin pump settings up-to-date and charged, and to switch to their home pump for any hospital admissions. Pump settings (basal rates, correction factors and carbohydrate ratios) could be optimized at any time during the study, per investigator discretion. If participants had ≥ 10% worsening of time in target glucose range or glucose time in range consistently below 50% compared to the run-in phase, they would be exited from the study. The study system was discontinued prior to hospital admission and delivery, and the participants resumed their personal pump therapy or were maintained on intravenous insulin infusion during delivery. Mothers provided consent for team review of newborn hospital records and study devices were returned after delivery.

Additional Details on Statistical Methods

All participants were included in all the analyses presented in the manuscript and Supplementary Material since the analyses were conducted on an intention-to-treat basis. The primary endpoint was the percent sensor glucose time in pregnancy-specific glucose target of 63 to 140 mg/dL (3.5-7.8 mmol/L). Primary and secondary glycemic outcomes from all participants were compared between run-in and CLC-P via

statistical testing. Shapiro-Wilk test was used to test normality in order to define the proper method to compare the outcomes from run-in versus CLC-P. For continuous variables, paired t-test was used when Shapiro-Wilk test revealed no evidence to reject the normality assumption (P>0.05), and Wilcoxon signed-rank test was used otherwise (P≤0.05). The only non-continuous outcome, hypoglycemic events, were modeled via Poisson regression with adjustment for the time offset and random participant effect.
A two-sided significance level of 0.05 was used for both primary and secondary outcomes. The p-values were calculated only for the outcomes that were pre-specified in the statistical analysis plan, and the primary outcome was not a safety outcome. Therefore, no multiplicity adjustment was applied in the analyses. Point estimates with 95% confidence intervals were reported for all analyses.

The models were not adjusted for any participant characteristic due to the small sample with a relatively similar participant characteristics for the variables that may influence the glycemic control outcomes (i.e., women at childbearing age with pre-existing type 1 diabetes and already using continuous glucose sensor and insulin pump). As such, no sub-group or sensitivity analyses were needed. Nonetheless, we provide outcomes for each participant in this Supplement.

Missing data were rare. We used only the available data in all the analyses and figures, as such missing data were not imputed. Data were processed in Matlab, Matlab 2019b. Statistical analyses were performed with R version 4.2.0.

Statistical power computations
There was no prior statistical power or sample size calculations for this study. We provide a post-hoc power analysis below in order to provide some insight about the detectable effect size expectations in a study that aims to evaluate improvement in glucose time in the target range for pregnant women with pre-existing type 1 diabetes.

Detectable relative change with hypothesized values from a previous similar study.

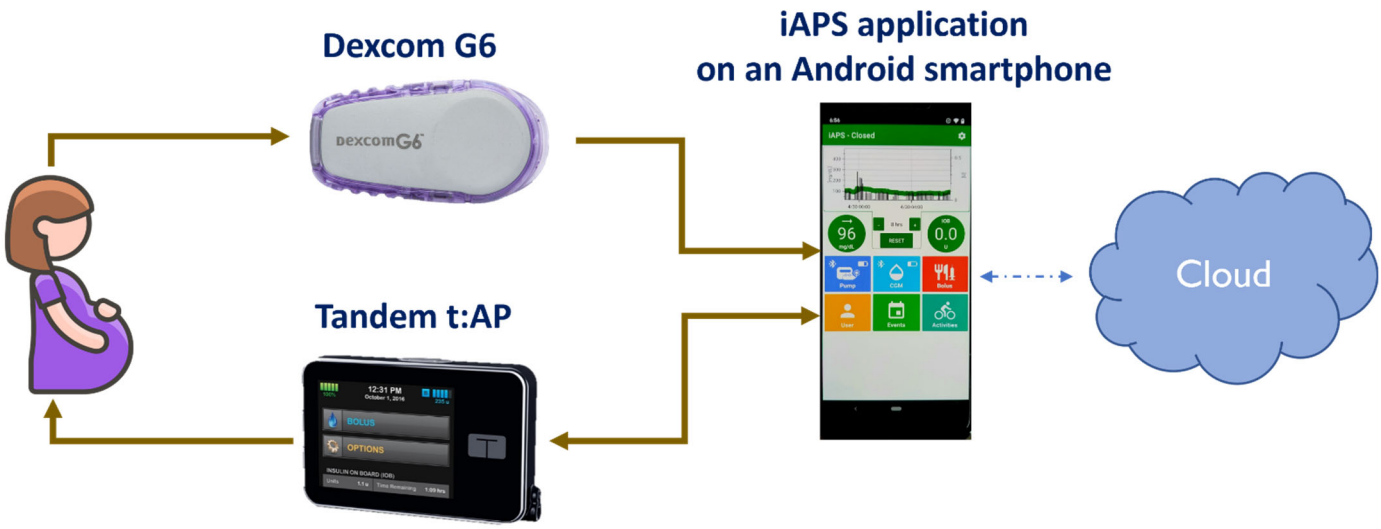
Power	N	Effect Size	Relative Change based on 59%±14%*
80%	10	1.0	24%
90%	10	1.2	28%
95%	10	1.3	31%

* Mean ± standard deviation from O'Malley et al[1]

We conducted a post-hoc power calculation using data from a previous similar study[1]. With our current sample of 10 participants, we were expected to detect the relative increase of 31% in the times that glucose levels were in the target range (from hypothesized baseline of 59% to 77%) with at least 95% power, using a two-tailed paired t-test at an alpha level of 0.05. The standard deviation for the primary outcome was assumed to be 14%.

[1] O'Malley G, Ozaslan B, Levy CJ, et al. Longitudinal observation of insulin use and glucose sensor metrics in pregnant women with type 1 diabetes using continuous glucose monitors and insulin pumps: the LOIS-P study. Diabetes Technol Ther 2021;23(12):807-817.

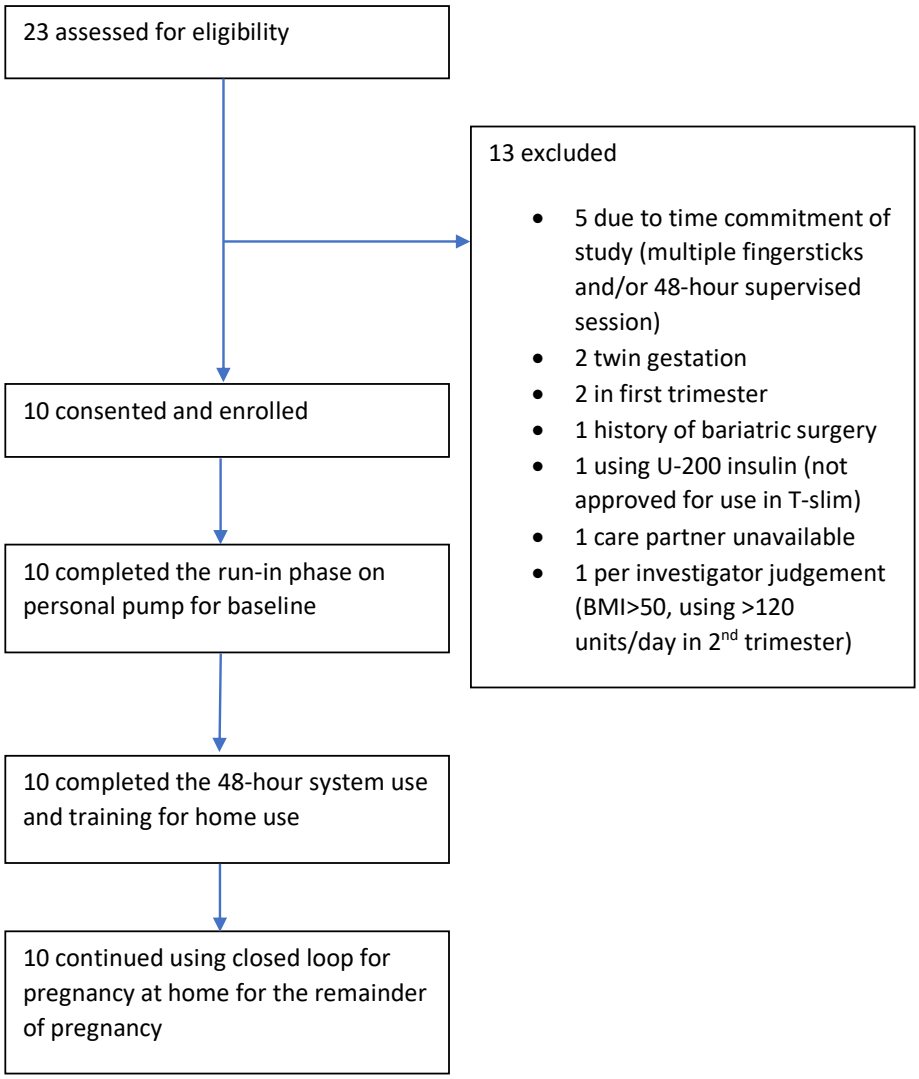
Supplemental Figure S1. Illustration of CLC-P system



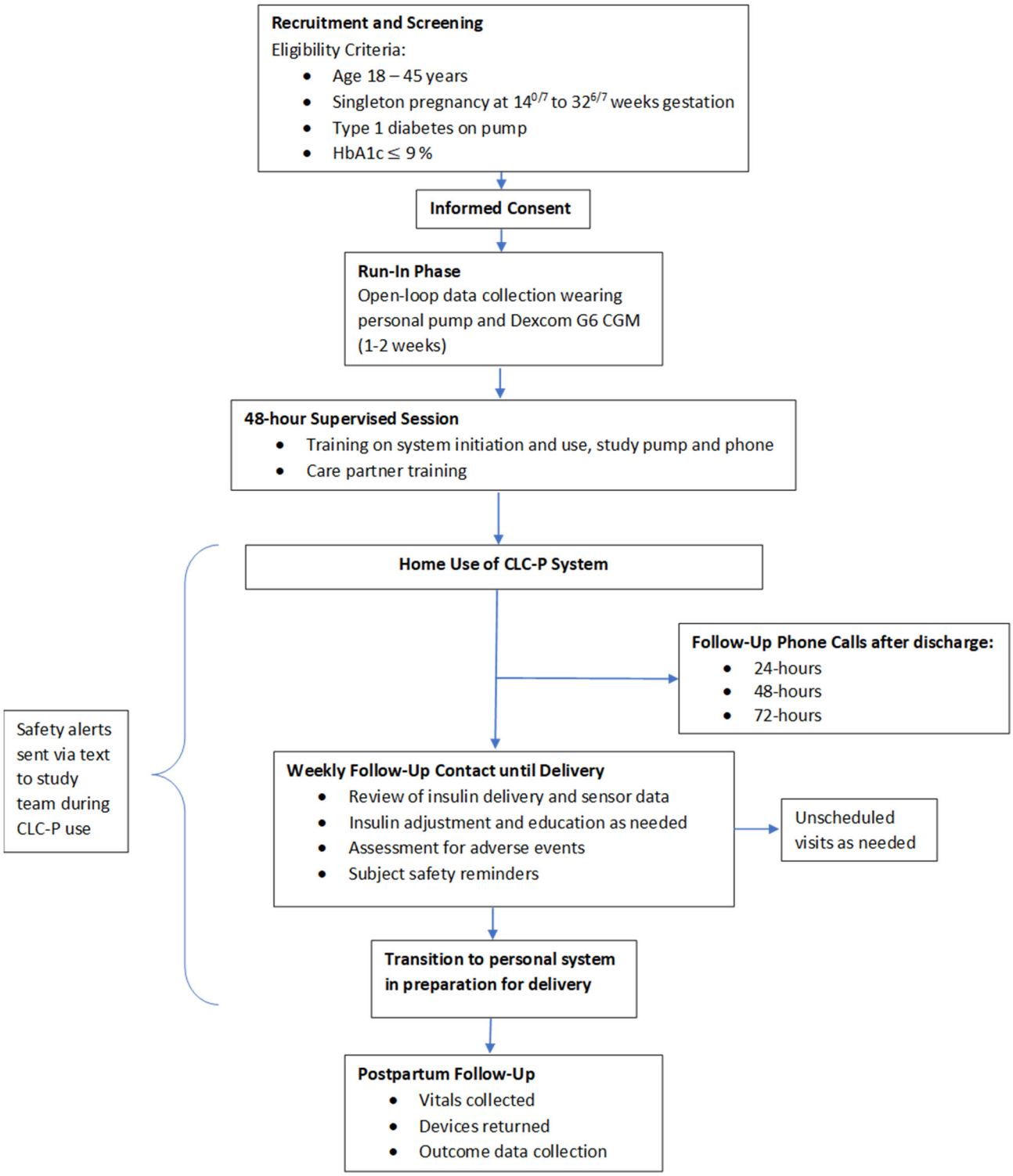
The iAPS is a novel, user-friendly, smartphone-based artificial pancreas platform integrating Dexcom G6 CGM and Tandem t:AP research insulin pump. The algorithms for AP glucose regulation namely the zone MPC for closed-loop insulin delivery and the HMS for predictive hypoglycemia alarms, run on the smartphone. As the iAPS[1] app resides in an unlocked smartphone and connects wirelessly to the continuous glucose monitor and the insulin pump, the complete system is portable. The app has an intuitive user interface allowing the participant to request an insulin bolus for meal/correction and the ability to log various activities such as rescue carbs and exercise. It also provides alarms for system malfunction such as loss of connectivity with devices, including text-messages to the study investigators for alarm events such as for impending hypoglycemia and prolonged hyperglycemia and hypoglycemia based on prespecified glucose thresholds and time periods. A web-based remote monitoring facility complements the app allowing the clinician to remotely initialize the system and verify salient features of participant's glycemic health.

[1]Deshpande S, Pinsker JE, Zavitsanou S, et al. Design and clinical evaluation of the Interoperable Artificial Pancreas System (iAPS) smartphone app: interoperable components with modular design for progressive artificial pancreas research and development. Diabetes Technol Ther 2019;21(1):35-43.

Supplemental Figure S2. CONSORT flow diagram



Supplemental Figure S3. Study Flow Diagram



Supplemental Table S1. Reasons for Unscheduled Visits

Reason for Visit	CLC-P	Run In
Participant had a potential device deficiency/issue	1	0
System connectivity issue	8	0
Insulin pump setting adjustment	56	5
Hyperglycemia*	20	0
Hypoglycemia (not defined as severe) *	7	0
Guidance transitioning on and off system †	4	0
Additional device training	5	0
Additional care partner training ‡	1	0
Total number of unscheduled visits ǂ	91	5

*Hyperglycemia and hypoglycemia contacts included topics such as real-time management of hyperglycemia/hypoglycemia and prevention of hyperglycemia/hypoglycemia. Severe Hypoglycemia was defined as an episode where a participant required assistance to treat a hypoglycemic event.

† Reasons for transitioning off and on of study system to personal system include travel outside of the United States and brief discontinuations for personal events.

‡Participant's usual care partner went away for travel, so a substitute care partner was trained.

ǂ Some unscheduled visits had more than one reason for contact, therefore, the total number of reasons (102 during CLC-P) exceeds the total number of unscheduled visits.

Supplemental Table S2. Details of Adverse Events and Adverse Device Effects

Gestational Age at Time of Event	Device Effect	SAE*	Description
$31^{4/7}$	No	No	Vaginal pruritis treated with 1-day terconazole.
$33^{3/7}$	No	No	Positive COVID-19 result. Mild symptoms and no medication taken for management.
$36^{6/7}$	Yes, related to insulin pump	No	Hyperglycemia and elevated ketones secondary to infusion set dislodgement. Infusion set was changed but suspected that there was subsequent occlusion as hyperglycemia was not resolving. Infusion set changed again and ketones and hyperglycemia resolved. Managed by site PI over phone and fully resolved same day. Highest fingerstick glucose during event was 313 mg/dl, and highest blood ketone level 1.4 mmol/l. No symptoms of DKA during event and did not require urgent care, emergency room or hospitalization.
$34^{2/7}$	Yes, related to insulin pump	No	Hyperglycemia and ketones due to infusion set issue. Participant was not home, and she did not have extra infusion set with her. She went home to replace the infusion set. When infusion set was replaced, fingerstick was 273 mg/dl and ketone level 2.0 mmol/l. Hyperglycemia and ketosis improved, and event did not require urgent care, emergency room or hospitalization.
$29^{4/7}$	No	No	Positive COVID-19 result. Mild symptoms and no medication taken for management.

*SAE denotes Serious Adverse Event

Supplemental Table S3. Participant Medical History and Personal Insulin Pump Type*

Participant ID	Pre-existing Medical Conditions	Insulin Pump During CGM Run-in
1	None reported	Tandem t:slim X2 with Basal-IQ
2	Generalized Anxiety Disorder, Hyperlipidemia	Tandem t:slim X2 with Control-IQ
3	Subclinical Hypothyroidism, Asthma	Tandem t:slim X2 (open loop)
4	Hypertension	Tandem t:slim X2 (open loop)
5	Vitiligo, Attention Deficit Disorder	Medtronic 670G (open loop)
6	Carpal Tunnel	Medtronic 670G (open loop)
7	Hashimoto's Thyroiditis	Tandem t:slim X2 with Basal-IQ
8	Retinopathy, Microalbuminuria	Omnipod Eros
9	Vitamin D Deficiency Hashimoto's Thyroiditis	Tandem t:slim X2 with Basal-IQ
10	Hashimoto's thyroiditis, Vitamin D Insufficiency, Lattice Degeneration	Omnipod Eros

*Pump systems being listed as "Open loop" denote the participant was not utilizing the pump's automated delivery option.

Supplemental Table S4. Primary and secondary glycemic control outcomes by participant[§]

ID	Phase	Mean glucose (mg/dL)	$HbA1_C$* (%)	% Time < 54 mg/dL	% Time < 63 mg/dL	% Time in 63-140 mg/dL	% Time > 140 mg/dL	% Time > 180 mg/dL	% Time > 250 mg/dL	Overnight % Time in 63-140 mg/dL[‡]	Postprandial two-hour % Time in 63-140 mg/dL[ŧ]	Hypoglycemic Events per Week**
1	Run-in	125.3	5.9	1.4	6.0	57.8	36.2	13.1	0.4	51.5	NA	4
	CLC-P	111.9	5.7	0.2	1.0	82.5	16.5	3.0	0.1	86.7	80.9	0.3
2	Run-in	97.7	6.6	0.8	4.5	87.0	8.5	2.9	0.0	90.3	NA	2
	CLC-P	101.0	6.2	0.5	2.3	88.9	8.8	1.1	0.0	89.7	86.4	0.8
3	Run-in	101.6	5.1	8.4	14.8	70.8	14.4	4.1	0.1	65.5	NA	12
	CLC-P	107.1	5.6	1.3	3.8	81.8	14.4	3.7	0.3	87.2	81.5	2.1
4	Run-in	135.7	6	0.0	0.2	58.3	41.4	10.0	0.0	84.7	NA	0
	CLC-P	116.0	5.6	0.3	1.5	77.6	20.9	4.7	0.2	87.3	69.7	0.4
5	Run-in	101.5	7	2.4	6.5	84.1	9.4	2.7	0.0	77.9	NA	7
	CLC-P	104.2	6.1	0.5	1.8	88.6	9.7	1.5	0.0	88.5	84.0	0.8
6	Run-in	93.3	5.5	6.3	19.1	72.2	8.7	4.5	2.2	60.2	NA	12
	CLC-P	110.1	5.6	0.4	2.2	84.2	13.6	3.1	0.1	90.8	78.1	0.8
7	Run-in	159.4	5.4	1.2	2.8	34.7	62.5	36.3	4.2	21.1	NA	2
	CLC-P	124.3	5.4	0.3	1.4	71.9	26.7	10.3	1.0	89.6	62.9	0.9
8	Run-in	128.8	5.6	0.6	2.6	64.8	32.7	13.8	1.1	40.3	NA	1
	CLC-P	124.3	5.8	0.4	1.6	70.5	27.8	9.1	0.8	74.9	68.0	0.5
9	Run-in	157.6	6.3	0.2	1.2	44.5	54.3	32.5	6.3	56.3	NA	0
	CLC-P	135.5	5.8	0.4	1.4	59.1	39.4	16.7	1.8	66.8	51.1	0.7
10	Run-in	129.6	5.1	0.0	0.0	70.3	29.7	3.9	0.0	65.1	NA	0
	CLC-P	116.5	5.2	0.1	0.4	80.8	18.8	3.0	0.1	86.1	71.4	0.1

[§] Plus minus values are mean ± standard deviation. ID denotes participant number. NA denotes not applicable. To convert values for glucose to millimoles per liter, multiply by 0.05551. The run-in week is defined as the last seven-days before the day participants switched to CLC-P. Participant #7's run-in was calculated based on their last eight days of data instead of seven days because they had one day missing within the last seven-days before switching to CLC-P.

*Reported CLC-P HbA1C is final $HbA1_C$ of the pregnancy

[‡] Overnight is defined as midnight to 6 AM.

[ŧ] Outcomes are calculated only for the CLC-P use period. Participants followed their regular treatment during run-in including how they reported their carbohydrate intake. Thus, postprandial outcome is calculated only for the CLC-P use, where participants were instructed to input all their carbohydrate intakes.

** Hypoglycemic events are defined as time <54 mg/dL for 15 consecutive minutes followed by time >70 mg/dL for 15 consecutive minutes. For CLC-P, number of hypoglycemic events per week is calculated by dividing the total number of events by the number of weeks participants was on CLC-P. Refer to Table S9 for the number of weeks that each participant was on CLC-P.

Supplemental Table S5. Closed-loop use and glucose sensor wear by participant

ID	Gestational age at enrollment	Gestational age at CLC-P start	Gestational age at CLC-P end	Percent Time in Closed Loop	Percent Time Sensor Connected	Number of Weeks on CLC-P
1	$15^{3/7}$	$16^{5/7}$	$37^{5/7}$	83.7%	98.1%	20.7
2	$21^{2/7}$	$25^{5/7}$	$36^{6/7}$	97.7%	99.1%	10.9
3	$22^{0/7}$	$23^{0/7}$	$37^{4/7}$	96.5%	98.7%	14.4
4	$26^{2/7}$	$27^{6/7}$	$37^{2/7}$	96.5%	98.9%	9.1
5	$18^{2/7}$	$20^{0/7}$	$37^{0/7}$	96.2%	97.6%	16.7
6	$23^{3/7}$	$25^{5/7}$	$37^{0/7}$	93.1%	99.0%	11.0
7	$20^{1/7}$	$21^{3/7}$	$39^{5/7}$	92.8%	98.6%	18.0
8	$23^{4/7}$	$24^{5/7}$	$37^{0/7}$	91.3%	98.3%	12.3
9	$26^{4/7}$	$27^{4/7}$	$39^{1/7}$	96.4%	99.0%	11.3
10	$23^{0/7}$	$24^{5/7}$	$39^{2/7}$	96.7%	97.3%	14.3

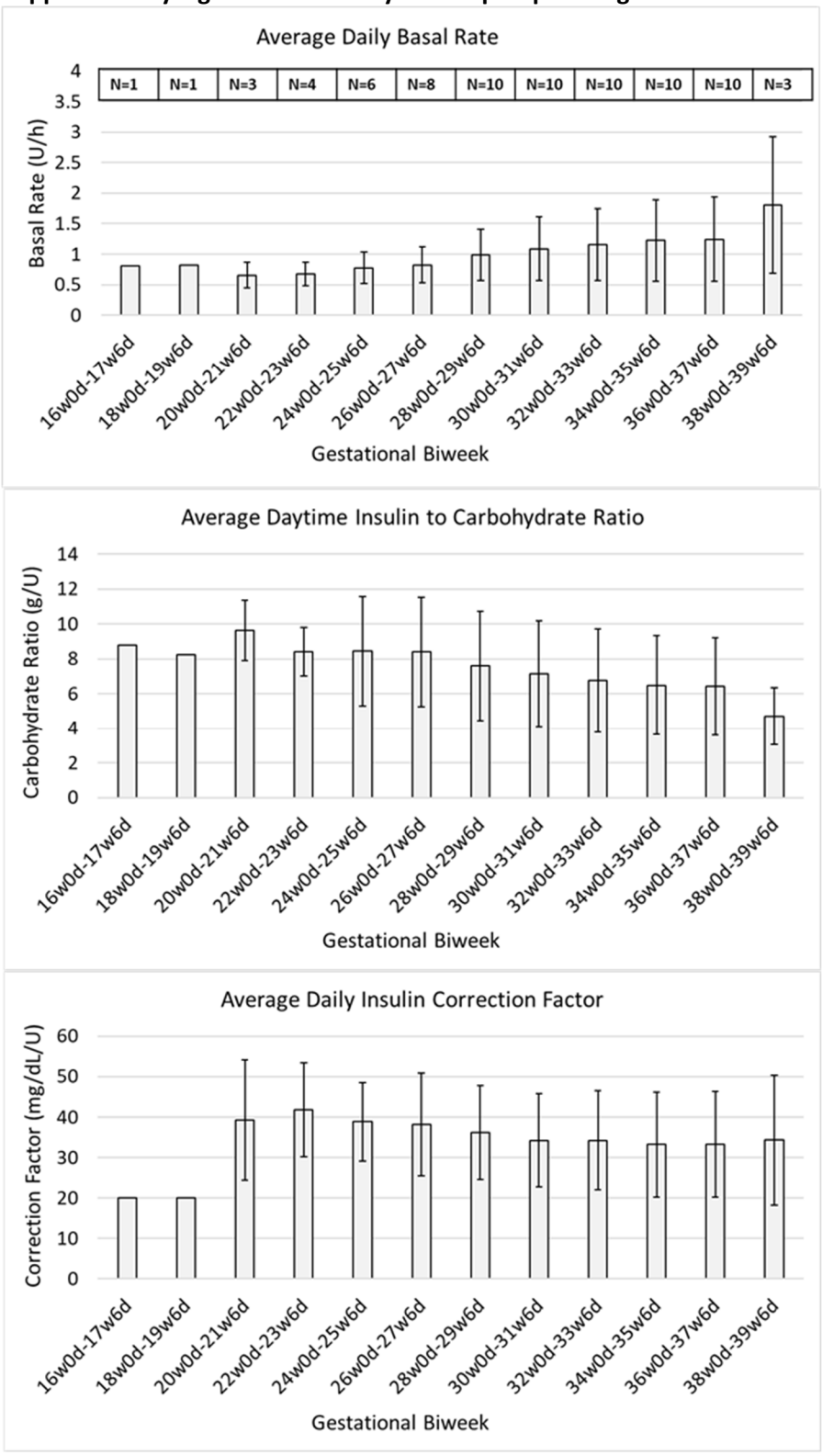
Supplemental Table S6. Daily insulin use during run-in and CLC-P by participant*

ID	Phase	Total Daily Dose (units per day)	Basal (units per day)	Bolus (units per day)	Basal:Bolus Ratio
1‡	Run-in	50.8	17.7	33.1±7.3	0.5
	CLC-P	63.9±15.9	26.6±6.9	37.3±12.9	0.8±0.4
2‡	Run-in	26.1	11.8	14.3±2.7	0.8
	CLC-P	34.7±5.0	16.6±2.1	18.1±4.3	1.0±0.3
3‡	Run-in	38.4	14.5	24.0±2.8	0.6
	CLC-P	62.2±19.4	14.1±1.9	48.2±19.3	0.3±0.2
4	Run-in	48.5±7.7	17.8±0.3	30.7±7.8	0.6±0.2
	CLC-P	50.1±6.5	19.8±2.2	30.3±5.4	0.7±0.1
5	Run-in	41.8±5.8	16.9±0.1	24.9±5.8	0.7±0.2
	CLC-P	56.0±16.7	22.1±3.8	34.0±14.6	0.8±0.3
6	Run-in	50.8±6.7	22.6±0.4	28.2±6.6	0.9±0.3
	CLC-P	52.4±6.3	25.5±3.7	26.9±5.3	1.0±0.3
7	Run-in	18.6±2.1	8.1±0.4	10.5±1.9	0.8±0.2
	CLC-P	23.5±3.0	11.6±2.1	12.0±2.3	1.0±0.3
8	Run-in	23.5±0.9	15.0±1.4	8.4±1.0	1.8±0.4
	CLC-P	24.5±4.8	15.8±3.0	8.7±2.6	2.0±0.8
9	Run-in	70.8±6.7	28.5±2.1	42.3±5.8	0.7±0.1
	CLC-P	90.0±11.3	40.5±4.0	49.5±10.2	0.9±0.2
10	Run-in	78.6±6.7	26.3±0.9	52.4±5.0	0.5±0.0
	CLC-P	100.5±26.7	38.1±9.0	62.4±19.4	0.6±0.2

*Plus minus values are mean ± standard deviation. For CLC-P, days with at least 20 hours of connection to the system and at least two bolus insulin are included. For run-in, all run-in days satisfied the at least 2 bolus insulin criteria and hence, all run-in days are included in the outcomes provided.

‡ Three participants had only weekly average basal insulin use available in their pump exports for the run-in period, as such standard deviations were not calculated for their basal dose, total daily insulin dose, and basal:bolus ratio.

Supplementary Figure S4. Biweekly insulin pump settings*



*Mean with standard deviation presented. The number of participants in each biweek varies due to variable gestational age at enrollment and delivery.

Supplemental Table S7. Individual obstetric history and maternal and neonatal outcomes*

Participant number	Gravidity	Parity	Prior Obstetric history	Gestational age at delivery	Antenatal steroids	Mode of delivery	Birthweight of Infant (g)	Neonatal hypoglycemia†	NICU	Neonatal complications	Obstetric complications
1	2	1	Late pre-term labor	$38^{0/7}$	No	SVD	3055	No	No	No	No
2	1	0	-	$38^{1/7}$	No	PCD (malpresentation)	2935	No IV dextrose. Glucose gel x 2. Resolved within 7 hours of delivery.	No	No	No
3	1	0	-	$37^{6/7}$	No	SVD	3430	No	No	No	No
4	4	3	HTN	$37^{3/7}$	No	SVD	3650	No	No	LGA	Postpartum hemorrhage‡ Exacerbation of HTN
5	2	1	-	$37^{1/7}$	No	SVD	3720	No	No	LGA	No
6	1	0	Gestational HTN	$37^{0/7}$	No	PCD (gestational HTN/ malpresentation)	3680	No IV dextrose. Glucose gel x 1. Resolved within 7 hours of delivery.	No	LGA	Gestational HTN
7	2	1	-	$39^{4/7}$	No	RCD	2880	No	No	SGA	No
8	1	0	-	$37^{0/7}$	Yes	PCD (fetal distress)	3065	No IV dextrose. Glucose gel x 3. Resolved within 12 hours of delivery.	No	No	No
9	3	1	First trimester miscarriage	$39^{1/7}$	No	RCD	3515	No	No	No	No
10	2	1	-	$39^{4/7}$	No	SVD	3941	No	Yes	Respiratory distress due to meconium aspiration	No

*NICU: Neonatal intensive care unit, SVD: spontaneous vaginal delivery, PCD: Primary Cesarean Delivery, RCD: Repeat Cesarean Delivery, HTN: Hypertension, SGA: small for gestational age, LGA: large for gestational age

† Neonatal hypoglycemia is defined as treatment requiring IV dextrose, treatment of the newborn with glucose gel is also reported, however protocols for use of glucose gel varied by delivery location.

‡ Postpartum hemorrhage >1