Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial

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OBJECTIVE

Despite advances in technology, optimal glucose control remains elusive and neonatal complications remain ubiquitous in type 1 diabetes (T1D) pregnancy. Our aim was to examine the safety, efficacy, and longer-term feasibility of day-and-night closed-loop insulin delivery.

RESEARCH DESIGN AND METHODS

We recruited 16 pregnant women (mean [SD]: age 32.8 [5.0] years, T1D duration 19.4 [10.2] years, HbA_{1c} 8.0% [1.1], and BMI 26.6 [4.4] kg/m^2) to an open-label, randomized, crossover trial. Participants completed 28 days of closed-loop and sensor-augmented pump (SAP) insulin delivery separated by a washout period. Afterward, participants could continue to use the closed-loop system up to 6 weeks postpartum. The primary end point was the proportion of time with glucose levels within the target range (63–140 mg/dL).

RESULTS

The proportion of time with glucose levels within target was comparable during closed-loop and SAP insulin delivery (62.3 vs. 60.1% [95% CI −4.1 to 8.3]; *P* = 0.47). Mean glucose and time spent hyperglycemic >140 mg/dL also did not differ (131.4 vs. 131.4 mg/dL [*P* = 0.85] and 36.6 vs. 36.1% [*P* = 0.86], respectively). During closed-loop, fewer hypoglycemic episodes occurred (median 8 [range 1–17] vs. 12.5 [1–53] over 28 days; *P* = 0.04) and less time at <63 mg/dL (1.6 vs. 2.7%; *P* = 0.02). Hypoglycemia <50 mg/dL (0.24 vs. 0.47%; *P* = 0.03) and low blood glucose index (1.0 vs. 1.4; *P* = 0.01) were lower. Less nocturnal hypoglycemia (2300–0700 h) during closed-loop therapy (1.1 vs. 2.7%; *P* = 0.008) and a trend toward higher overnight time in target (67.7 vs. 60.6%; *P* = 0.06) were found.

CONCLUSIONS

Closed-loop insulin delivery was associated with comparable glucose control and significantly less hypoglycemia than SAP therapy. Larger, longer-duration multicenter trials are now indicated to determine clinical efficacy of closed-loop insulin delivery in T1D pregnancy and the impact on neonatal outcomes.

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Type 1 diabetes (T1D) in pregnancy is associated with an increased risk of maternal and neonatal complications (1–3). These complications, attributed to greater fetal exposure to maternal hyperglycemia, occur more commonly in women with suboptimal glucose control (4). Thus, the primary focus of treatment in a T1D pregnancy is to reduce fetal exposure to hyperglycemia without increasing maternal hypoglycemia. Recent evidence has suggested that although continuous glucose monitoring (CGM) improves day-to-day glucose control, with ~1 h/day less hyperglycemia in women who use multiple daily injections (MDIs) and continuous subcutaneous insulin infusion (CSII), optimal maternal glycemia is not achieved (5).

Even with increasing use of new CGM and CSII technologies, pregnant women with T1D continue to spend, on average, 8 h/day hyperglycemic (5,6). Furthermore, two-thirds of T1D offspring have complications related to maternal hyperglycemia, including large for gestational age and preterm delivery, which contribute to high rates of neonatal intensive care unit admissions (4,5).

Hybrid closed-loop insulin delivery (artificial pancreas) systems provide automated glucose-responsive insulin delivery between meals and overnight with manually triggered premeal doses (7). Closed-loop systems have been evaluated in children, adolescent, and adult populations under inpatient, outpatient, and home conditions and are associated with reduced exposure to hyperglycemia and hypoglycemia (8,9). Short-term studies in nonpregnant adults with near-optimal glucose control (HbA_{1c} < 7.5%) have suggested a potential for reduced hypoglycemia (10). A recent systematic review and meta-analyses in 585 participants across 27 outpatient studies found consistent improvements in glucose control across a wide variety of clinical settings and closed-loop systems (11).

Closed-loop insulin delivery may be useful in T1D pregnancy, when glucose control targets are tighter and the burden of hypoglycemia is greater (12). The physiological changes in insulin sensitivity and day-to-day variability in insulin pharmacokinetics make achieving near-optimal glycemia challenging (7,13). Our recent trial of overnight closed-loop insulin delivery found a 15% increased time in target (75 vs. 60%; P = 0.002) between 2300 and 0700 h with closed-loop versus sensor-augmented pump (SAP) therapy (14,15). However, achieving optimal glucose control is substantially more challenging during the daytime when meals, snacks, and exercise require manual premeal boluses with or without basal dose adjustment (16). Because hybrid closed-loop systems adjust only basal insulin, the potential role that day-and-night closed-loop systems play in T1D pregnancy is unknown. Our aim was to evaluate the safety, efficacy, and longer-term feasibility of day-and-night closed-loop insulin delivery in pregnant women with T1D.

RESEARCH DESIGN AND METHODS

Study Design

The trial was an open-label, randomized, two-period crossover study in pregnant women that assessed the safety, efficacy, and longer-term feasibility of day-and-night closed-loop versus SAP therapy during T1D pregnancy. After providing written informed consent, participants were trained on the use of the study CGM (FreeStyle Navigator II; Abbott Diabetes Care, Alameda, CA) and pump (DANA Diabecare R; Sooil, Seoul, Republic of Korea) devices and practiced using them for 2–4 weeks before completing a device competency assessment. Participants were randomly assigned to either 4 weeks of closed-loop (intervention) insulin delivery or 4 weeks of real-time CGM and CSII without the closed-loop system (SAP control). At the end of the first phase was a 1- to 2-week washout period before participants crossed to the alternate phase. After the randomized trial, participants could choose to resume their previous intensive insulin therapy or continue to use the study devices (any combination of CGM, pump, or closed-loop) throughout pregnancy and delivery and for up to 6 weeks postpartum. As in our previous overnight closed-loop study, this pragmatic extension provided a longer-term feasibility assessment and minimized ethical concerns about discontinuing a potentially beneficial treatment during pregnancy (14).

The randomization schedule was created with an automated Web-based program that used a permuted four-block schedule maintained in a secure database, ensuring that allocation was concealed from trial staff and participants. Participants were recruited from three U.K. National Health Service (NHS) antenatal clinics (Cambridge, Norwich, and Ipswich). Women participated from within the home and antenatal clinic setting, with 24-h support provided by the research team throughout the study.

Capillary glucose testing was recommended at least seven times daily with National Institute for Health and Clinical Excellence glucose targets in both groups of 63–99 mg/dL premeal and < 140 mg/dL 1 h postmeal. No restrictions were placed on exercise, meals, or overseas travel, and no remote monitoring was used. Participants had antenatal clinic visits every 2 weeks.

HbA_{1c} outcome measurements were taken at randomization; the end of each crossover period; at 28, 32, and 36 weeks' gestation; and 6 weeks after delivery. They were analyzed at a central laboratory (Addenbrooke's Hospital, Cambridge, U.K.) using an International Federation of Clinical Chemistry and Laboratory Medicine–aligned method (G7 HPLC Analyzer; Tosoh Bioscience) (interassay coefficient of variance 3.71% at HbA_{1c} 5.41% and 1.7% at HbA_{1c} 10.6%). Quality and quantity of sleep were assessed with the Pittsburgh Sleep Quality Index, a sleep diary, and actigraphy (Actiwatch; Philips Respironics) (17). Participants completed questionnaires (Diabetes Technology Questionnaire and Hypoglycemia Fear Survey) at baseline and at the end of each crossover (18,19). Reportable adverse events included all serious adverse events other than prespecified protocol exceptions.

Study Participants

We recruited pregnant women who had T1D for at least 1 year before pregnancy. They were age 18–45 years and had a singleton pregnancy with ultrasound-confirmed gestational age between 8 and 24 weeks. Participants had had intensive insulin treatment (either MDI or CSII) and a booking HbA_{1c} (measurement taken at the first antenatal clinic visit after confirmed pregnancy) level of ≥6.5 and ≤10% (≥48 and ≤86 mmol/mol). Participants were required to speak and understand English and to have e-mail access. Exclusion criteria were a physical or psychological disease likely to interfere with the conduct of the study, medications known to interfere with glucose metabolism, and an insulin dose of ≥1.5 units/kg.

Study Oversight

The study protocol was approved by the Health Research Authority, East of England

Regional Ethics Committee (London, U.K.) (15/EE/0278), with notification of no objection provided by the Medicines and Healthcare Products Regulatory Agency (London, U.K.) (CI/2015/0042). All participants provided written informed consent. Details of the protocol and prespecified trial outcomes are available on the International Standard Randomized Controlled Trial Number register (ISRCTN83316328).

Closed-Loop System

The closed-loop system (Florence D2A; University of Cambridge, Cambridge, U.K.) used CGM glucose measurements to automatically adjust insulin rates. Real-time glucose readings were transmitted using Bluetooth through a purpose-built translator to an android mobile phone (Samsung Galaxy S4; Samsung, Daegu, Republic of Korea), which housed the algorithm. The control algorithm (Florence D2A, version 0.3.41p; University of Cambridge) aimed for interstitial glucose levels of 104.4–131.4 mg/dL, adjusting for fasting and postmeal conditions and for accuracy of glucose prediction. The control algorithm included enhanced adaptation of insulin needs on the basis of identification of the time of day compared with that used in our previous overnight home study (14) and is not substantially different from the usual Cambridge algorithm used in studies outside of pregnancy (10).

The algorithm incorporated learning about day-to-day insulin doses and adapted insulin delivery for particular times of day when individual participant requirements were higher or lower. Every 12 min, the insulin dose was communicated through Bluetooth to the DANA pump, which delivered insulin. The DANA pumps were modified in-house (replacement caps inserted) to allow participants to select their preferred infusion set from a range of commercially available consumables from Medtronic (Northridge, CA) and Animas (West Chester, PA).

Premeal insulin boluses were given manually 15–30 min before eating by using the pump's bolus calculator. To initialize the closed-loop system, the participant's weight and total daily insulin dose were entered manually, with insulin pump settings automatically transferred through Bluetooth. Safety rules limited maximum insulin dose and suspended insulin delivery when glucose levels fell rapidly and/or were $<$77.4 mg/dL. Capillary glucose calibration tests were advised twice daily (before breakfast and the evening meal). Recalibration of CGM was recommended if sensor and capillary glucose levels differed by $\geq$54 mg/dL.

At the start of closed-loop therapy, participants had a device training session (30–60 min) that included instructions for starting and stopping the system and troubleshooting for technical issues. During the randomized trial and follow-up, participants were advised to use the closed-loop device continuously. To maintain device connectivity, participants had to be within ~30 m of the device. There were no changes to announce for antenatal corticosteroids, labor, or delivery, but the nonpregnant glucose targets (70–180 mg/dL) were applied immediately postpartum. Participants had access to a 24-h phone line staffed by the research team.

Study End Points

Safety end points were nocturnal (2300–0700 h) and/or severe hypoglycemic episodes (defined as requiring third-party assistance and/or capillary glucose $<$50 mg/dL associated with clinical symptoms) and other adverse events. The primary efficacy end point was the percentage of time spent within the T1D pregnancy target range (63–140 mg/dL) as measured by CGM during the 4-week intervention periods. Prespecified secondary glycemic outcomes derived from CGM measures included mean glucose, time $>$140 and $>$180 mg/dL (to quantify fetal hyperglycemic exposure), time $<$63 and $<$50 mg/dL (to quantify maternal hypoglycemia), maternal hypoglycemic episodes ($<$63 mg/dL for $\geq$20 min), low blood glucose index (LBGI) to quantify hypoglycemia duration and extent (20), and SD to quantify glucose variability. Additional outcomes were central laboratory HbA_{1c}, time in nonpregnant target range (70–180 mg/dL), CGM compliance, total insulin dose, questionnaires, and measures of sleep.

The longer-term feasibility of day-and-night closed-loop insulin delivery (from the end of the randomized trial until delivery) was assessed by CGM measures during prespecified intervals (28–32 weeks, 32–36 weeks, and from 36 weeks until delivery). The glucose target range was adjusted to 70–180 mg/dL (nonpregnant) during the assessment period from after delivery until up to 6 weeks postpartum.

Statistical Analysis

Previous study participants who used SAP therapy spent a mean (SD) of 61.7% (24.9%) time in target (16,21). To detect a 30% relative increase (62–80%), we estimated that a sample size of 16 participants was needed to achieve 80% power and an α-level of 0.05 (two-tailed). The SD of the primary outcome was assumed to be 25% (16,21).

Statistical analyses were performed on an intention-to-treat basis. A 5% significance level was used for all comparisons without adjustment for multiplicity. Outcomes were calculated with Gstat version 2.2 software (University of Cambridge), and statistical analyses were performed using SPSS and R. Results during the randomized crossover study phases were compared using linear mixed-effects models, with the response variable being time in target and the study arm as a fixed effect and study participant and 4-week block as nested random effects.

RESULTS

Study Participants

Nineteen participants were recruited to the study (Fig. 1). Of these, two withdrew before randomization (one disliked the study pump, and one experienced mental health deterioration), and one withdrew as a result of pregnancy complications. This participant had preterm premature rupture of membranes with severe oligohydramnios during her first (SAP) study phase. She underwent an elective termination of pregnancy and was withdrawn at 20 weeks' gestation. Sixteen participants completed the randomized crossover trial and are included in the analyses. Their baseline characteristics are shown in Table 1, with equal numbers of pump and MDI users and nine (56%) with suboptimal HbA_{1c}.

Randomized Crossover Trial Outcomes

No difference was found in the primary outcome of percentage of time in the target glucose range (63–140 mg/dL) during closed-loop and SAP therapy (62.3 vs. 60.1%, absolute difference 2.1% [95% CI $-$4.1 to 8.3]; P = 0.47) (Table 2). Likewise, mean glucose and time spent hyperglycemic ($>$140 mg/dL) did not differ between closed-loop and SAP therapy (131.4 vs. 131.4 mg/dL [P = 0.85] and 36.6 vs. 36.1% [P = 0.86], respectively). During the 4 weeks of closed-loop therapy, fewer episodes of maternal hypoglycemia occurred (median 8 [range 1–17] vs. 12.5

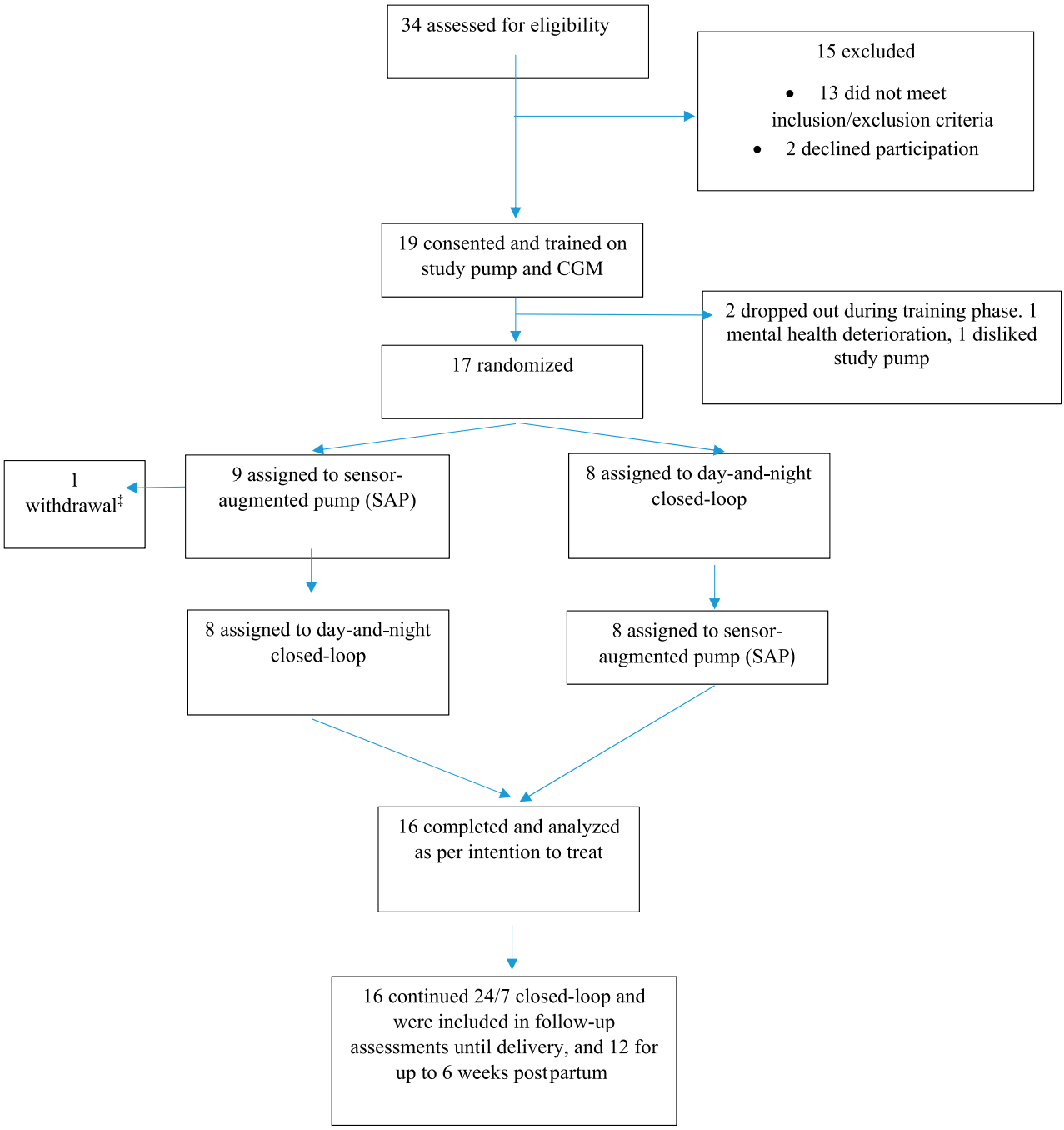

Figure 1—CONSORT flow diagram. ‡Withdrawal as a result of preterm premature rupture of membranes, severe oligohydramnios, and termination of pregnancy because of poor fetal prognosis.

[1–53]; P = 0.04) and less time was spent <63 mg/dL (1.6 vs. 2.7% [95% CI −0.2 to −2.1]; P = 0.02). Time <50 mg/dL (0.24 vs. 0.47% [95% CI −0.02 to −0.5]; P = 0.03) and LBGI (1.0 vs. 1.4 [95% CI −0.7 to −0.1]; P = 0.01) were lower during closed-loop therapy.

There was less overnight time (2300–0700 h) <63 mg/dL during closed-loop insulin delivery (1.1 vs. 2.7% [95% CI −2.8 to −0.4]; P = 0.008). The overnight time in target was also higher during closed-loop therapy, but this difference did not reach statistical significance (67.7 vs. 60.6% [95% CI −0.8 to 15.2]; P = 0.06) (Supplementary Table 1).

No episodes of severe hypoglycemia occurred. The mean (SD) HbA_{1c} was 6.6% (2.8) (48.5 mmol/mol [7.5]), 6.4% (2.7) (46.3 mmol/mol [5.6]), and 6.3% (2.7) (45.9 mmol/mol [5.5]) at baseline, end of closed-loop, and end of SAP therapy, respectively. During closed-loop and SAP therapy, no difference was found in HbA_{1c} between baseline and the end of each study phase (P = 0.15 and 0.14, respectively) and no difference was found in HbA_{1c} between the systems (P = 0.67). No differences were found in total insulin doses, although basal insulin delivery was, as expected, more variable during closed-loop therapy (SD 0.1 vs. 0.8 units/kg/day; P < 0.0001) (Supplementary Table 2).

Table 1—Baseline characteristics of trial participants ($N = 16$)

	n (%)	Mean (SD)
Age (years)		32.8 (5.0)
BMI (kg/m^2)		26.6 (4.4)
Booking HbA_{1c} (%)†		8.0 (1.1)
Booking HbA_{1c} (mmol/mol)		63.7 (12.1)
Booking HbA_{1c} >7.5% (58 mmol/mol)	9 (56)	
Duration of diabetes (years)		19.4 (10.2)
Insulin pump use before study	8 (50)	
CGM use before study±	3 (19)	
Total daily insulin dose (units/kg/day)		0.51 (0.09)
Weeks' gestation*		16.4 (4.9)
Primiparous‡	6 (38)	
Recruitment site		
Cambridge	6 (38)	
Norwich	8 (50)	
Ipswich	2 (12)	

†The booking HbA_{1c} is the measurement taken at the first antenatal clinic visit after confirmed pregnancy. ±None of the three participants had used CGM in the 6 months before enrollment in the study or as part of their regular diabetes management. Two had used real-time CGM (participant 6 and participant 12) and one FreeStyle Libre (participant 15). *Weeks' gestation at randomization. Randomization was performed after recruitment and at least 2–4 weeks of device training when insulin regimens were optimized and participants were competent in using the study pump and CGM devices. ‡Six participants had experienced previous pregnancy losses (six miscarriages and one stillbirth). Two participants had had a termination of pregnancy for major malformation. Two participants had a history of hypertensive disorders of pregnancy.

Quality and quantity of sleep were comparable, with a sleep duration (mean [SD]) of 7.5 h (0.8) during closed-loop therapy and 7.1 h (1.2) during SAP therapy ($P = 0.22$). No differences were found in the patient-reported questionnaires. Most participants (>80% at the end of both phases) reported less fear of nocturnal hypoglycemia, although more than one-third experienced ongoing worry or fear about low blood sugar during sleep.

No reportable serious adverse events occurred, but there were frequent device deficiencies, which most frequently involved the closed-loop mobile phone (47%) and CGM (30%) devices. Fewer concerns existed about the insulin pump (13%) and device downloads (10%) (Supplementary Table 3).

Longer-term Antenatal Feasibility

All participants chose to continue to use the closed-loop system for at least some of the time after the randomized trial, with median time in target of 70.6% (16.9 h/day) between 28 and 32 weeks' gestation, 71.5% (17.2 h/day) between 32 and 36 weeks, and 72.3% (17.4 h/day) from 36 weeks until delivery (Fig. 2 and Table 3). Participant 8 traveled to the Middle East for 8 weeks without contact or antenatal care. Participant 15 relocated to Australia and continued with closed-loop therapy until delivery. Details of individual participant's glucose control are shown in Fig. 2.

Postpartum Closed-Loop Feasibility

After delivery, 12 participants chose to continue to use the closed-loop system. They maintained safe glucose control, with 77.1% time in target (70–180 mg/dL) and minimal hypoglycemia (2.3% <70 mg/dL) during the first 6 weeks postpartum (Table 3). Sensor wear was variable after delivery, with a median of 16.5 h/day. Where postpartum sensor wear was low, generally, the participant used CGM for the life span of a sensor, with gaps between the expired use of one sensor and the insertion of a new one (Supplementary Table 4).

Obstetric and Neonatal Outcomes

Participants delivered at a median gestation of 36.9 weeks (interquartile range [IQR] 36.1, 37.8). Thirteen delivered by cesarean section, seven of whom delivered before the onset of labor. Two participants developed preeclampsia. One participant had a placental abruption. The median neonatal birth weight was 3,575 g (IQR 3,073, 3,745). Seven (44%) infants were large for gestational age (≥90th percentile), with five ≥97th percentile. One neonate, born to a mother with excellent glucose control (participant 7), was small for gestational age (birth weight 2,880 g) but was healthy and without

Table 2—Glycemic outcomes of trial participants

	SAP	Closed-loop	Absolute difference (95% CI)	*P* value
Crossover phase time in T1D pregnancy target range (%)*	60.1	62.3	2.1 (−4.1 to 8.3)	0.47
Secondary glycemic outcome				
Mean CGM glucose (mg/dL)	131.4	131.4	0 (−0.3 to 0.4)	0.85
Time >140 mg/dL or 7.8 mmol/L (%)	36.6	36.1	−0.6 (−7.4 to 6.3)	0.86
Time >180 mg/dL or 10 mmol/L (%)	14.8	14.6	−0.1 (−4.2 to 4.0)	0.94
Time <63 mg/dL or 3.5 mmol/L (%)	**2.7**	**1.6**	**−1.1 (−0.2 to −2.1)**	**0.02**
Time 50 mg/dL or <2.8 mmol/L (%)	**0.5**	**0.2**	**−0.2 (−0.0 to −0.5)**	**0.03**
Hypoglycemic events >28 days	**12.5 (1–53)**	**8 (1–17)**		**0.04**
LBGI±	**1.4**	**1.0**	**−0.4 (−0.7 to −0.1)**	**0.01**
SD of sensor glucose (mg/dL)	37.8	36.0	−12.6 (−3.6 to 1.8)	0.29
TDD insulin (units/day)	41.5	43.7	2.2 (−6.4 to 0.7)	0.56
Sensor wear (h/day)	20.3	20.2		

Data are derived from linear mixed-effects models except for number of hypoglycemic events, which are median (range) and defined as sensor glucose values <63 mg/dL for ≥20 min. Significantly different data appear in boldface type. TDD, total daily dose. *The primary efficacy end point was the percentage of time that glucose was in the T1D pregnancy target range of 63–140 mg/dL (3.5–7.8 mmol/L) as recorded by CGM during each 4-week study phase. ±The LBGI assessed the duration and extent of hypoglycemia.

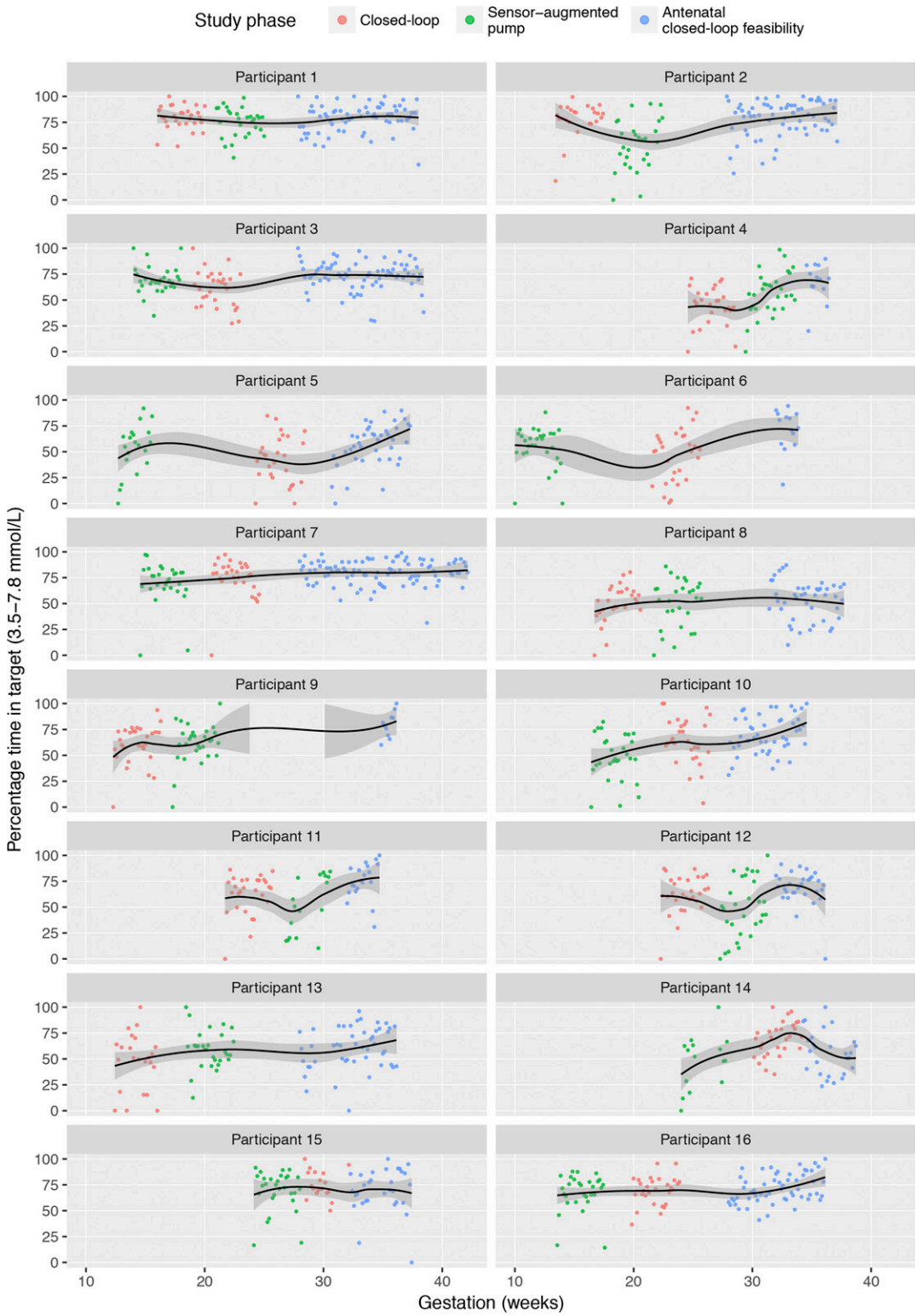

Figure 2—Glycemic control during the randomized crossover trial and antenatal closed-loop feasibility phase by individual participant.

complications. Eleven (69%) infants were admitted to the neonatal intensive care unit, with seven (44%) treated for hypoglycemia (Supplementary Tables 5 and 6).

Two infants had congenital anomalies. One had a neural tube defect (lumbar/sacral lipomyelomeningocele) detected postpartum. This mother (participant 2) had an unplanned pregnancy (booking HbA_{1c} 8.1%), switched from MDI to the closed-loop system with good effect, and maintained excellent glucose control throughout pregnancy. Another infant had severe unilateral hydronephrosis (10-mm renal pelviceal dilatation detected at 20 weeks' gestation). This mother (participant 8, with booking HbA_{1c} 9.7%), who conceived spontaneously after four unsuccessful

Table 3—Glycemic control during the antenatal and postpartum closed-loop feasibility phases±

	Antenatal feasibility			Postnatal feasibility
	28–32 weeks' gestation	32–36 weeks' gestation	>36 weeks' gestation	0–6 weeks
Participants (*n*)	8	16	9	12
Time in target range* (%)	70.6 (64.2, 75.4)	71.5 (68.9,75.9)	72.3 (67.3, 80.3)	77.1 (75.1, 90.4)
Time above target range (%)	28.0 (23.0, 34.0)	24.4 (22.8, 29.3)	23.7 (17.7, 31.5)	22.1 (9.5, 24.4)
Time below target range (%)	1.9 (1.7, 2.3)	2.0 (1.1, 3.9)	2.3 (1.0, 3.0)	2.4 (0.8, 3.7)
Mean glucose (mg/dL)	124.2 (118.8, 129.6)	120.6 (115.2, 124.2)	118.8 (115.2, 124.2)	138.6 (127.8, 147.6)
Sensor wear (h/day)	22.4 (11.3, 23.2)	19.9 (15.1, 23.0)	NA	16.5 (11.6, 19.2)

Data are median (IQR) unless otherwise indicated. NA, not applicable. ±The antenatal closed-loop feasibility phase was from the end of the randomized crossover trial until delivery. The postnatal closed-loop feasibility phase was from delivery up to 6 weeks postpartum. *The glucose target range was 63–140 mg/dL (3.5–7.8 mmol/L) during pregnancy and 70–180 mg/dL (3.9–10.0 mmol/L) after delivery.

cycles of in vitro fertilization, also switched from MDI to the closed-loop system and experienced a striking fall in HbA_{1c} (5.0%) despite modest time in target (56%) in late pregnancy (Supplementary Tables 5 and 6).

Interindividual Variability

The individual participant data highlight variability in the participants' glycemic responses to closed-loop insulin delivery (Fig. 2), which does not appear to be related to previous technology use because glycemic control was comparable in participants who used CSII or MDI at enrollment (Supplementary Table 7). Five (31%) participants spent less time in target and had higher mean glucose levels during closed-loop therapy. These included two CSII (participants 3 and 5) and three MDI (participants 4, 6, and 13) users who had ≥10% lower time in target during the closed-loop crossover, although they all continued to use the closed-loop system, with higher time in target, in later pregnancy.

Post hoc analyses suggested that participants with lower booking HbA_{1c} levels (≤7.5%) had higher time in target during both closed-loop and SAP phases compared with those with HbA_{1c} >7.5% (Table 4). This pattern persisted throughout pregnancy, including after 36 weeks, when participants with lower HbA_{1c} in early pregnancy maintained excellent glucose control (mean glucose 115 mg/dL, 78% equivalent to 18.7 h/day in target). Participants with suboptimal glucose control in early pregnancy had higher mean glucose and lower time in target, even after 36 weeks' gestation (at 126 mg/dL, 69% in target or 16.6 h/day).

CONCLUSIONS

We found that day-and-night closed-loop insulin delivery is safe and could effectively control glucose levels in a broad range of pregnant women with T1D. Participants achieved comparable glucose control during SAP and closed-loop therapy, with no between-group differences in time in target, mean glucose, or HbA_{1c} levels. A reduction was observed in frequency of maternal hypoglycemic events and reduced exposure both to overall and to nocturnal hypoglycemia during closed-loop delivery.

The current study is part of a phased program of developing and evaluating closed-loop insulin delivery in pregnancy. The first nonrandomized, proof-of-concept study (*n* = 10 participants) demonstrated the ability of closed-loop to adjust overnight insulin delivery in early and late gestation in a closely supervised clinical research facility setting (21). The second study (*n* = 12 participants) compared day-and-night closed-loop with SAP insulin delivery for >24 h in the clinical research facility (16). The third was the first home study of overnight closed-loop therapy with the same sample size (*n* = 16), randomized crossover design, SAP comparator, and duration of intervention as the current study (14). The stepwise progression from clinical research facility to home and from overnight to day and night is necessary to document initial safety and feasibility before proceeding with a pivotal clinical trial.

A recent systematic review found that outside pregnancy, closed-loop insulin delivery is associated with a 12.6% increased time in target range, when the comparator group (SAP users in 21 of 22 single-hormone closed-loop studies) spent 58% of time (13.3 h/day) in the wider glucose target range of 70–180 mg/dL (11). In the current study where both groups were at >60% of the time in target range (63–140 mg/dL for T1D pregnancy), no further improvement was obtained. Our previous study of overnight closed-loop insulin delivery in pregnancy (14) also found that compared with SAP, the closed-loop system was associated with a 15% higher time in target (75 vs. 60%; $P < 0.002$). In the current study, participants who used SAP achieved comparable overnight glucose control, but the closed-loop effect was less, with a 7% nonsignificant increase (68 vs. 61%; $P = 0.06$).

Several potential explanations exist for the current findings. First, the level of glucose control achieved with SAP (60% in 70–140 mg/dL, 82.5% in 70–180 mg/dL) in pregnancy is considerably higher than in previous studies outside pregnancy (8,9,11). The glucose control achieved with SAP in this study was comparable or higher than that achieved with the closed-loop system previously (8,9), including in adults with well-controlled levels (HbA_{1c} <7.5%), thereby minimizing the potential for further improvement (10). The role of closed-loop insulin delivery in adults with well-controlled glucose levels may be to reduce the burden of hypoglycemia without deterioration in glucose control.

Second, the small sample size of this phase 2a study meant that we lacked statistical power for anything other than the power calculation assumption of a 30% between-group difference. Recent results from a CGM trial in 215 T1D pregnancies suggested that even small differences (a 7% increase in time in target and 5% reduction in hyperglycemia in the Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial [CONCEPTT]) are associated with substantial (~50%) reductions in neonatal complications (5). The current study was underpowered to detect small differences.

Third, we consciously enrolled a broad patient population for this study, including

Table 4—Glycemic control during the randomized crossover trial and antenatal closed-loop feasibility phase in participants with booking HbA_{1c} levels ≤7.5% or >7.5% (58 mmol/mol)

	Booking HbA_{1c} ≤7.5% (n = 7)†						Booking HbA_{1c} >7.5% (n = 9)†					
	SAP	CL	Difference (CL − SAP)	28–32 weeks' gestation	32–36 weeks' gestation	>36 weeks' gestation	SAP	CL	Difference (CL − SAP)	28–32 weeks' gestation	32–36 weeks' gestation	>36 weeks' gestation
Time in target (63–140 mg/dL) (%)	69.1*	72.1*	3	72.0	74.0	77.7*	57.0*	57.3*	0.3	64.6	69.0	68.8*
Time <63 mg/dL (%)	1.0	0	−1.0	1.6	2.7	4.1*	0	0.2	0.2	3.0	2.6	1.5*
Mean glucose (mg/dL)	122.4*	120.6*	−1.8	122.4	117.0	115.2*	136.8*	142.2*	5.4	127.8	124.2	126.0*

CL, closed-loop. †The booking HbA_{1c} is the measurement taken at the first antenatal clinic visit after confirmed pregnancy. *Indicates significant difference between participants with HbA_{1c} ≤7.5% and booking HbA_{1c} >7.5% ($P < 0.05$).

women with variable levels of technology experience, diabetes education, and glycemic control. The majority were technology naive, with >80% sensor naive and 50% pump naive at enrollment. More than one-half had suboptimal booking HbA_{1c} levels, defined as >7.5%. Among the five participants with lower time in target during closed-loop therapy, one cycled 30–60 min twice daily and struggled to avoid postexercise hypoglycemia (participant 3), whereas another who worked as an events planner had more night shifts during the closed-loop phase (participant 4). Three participants (4, 6, and 13) were frequent nonattenders at antenatal clinics and had minimal contact with the research team. All three used the closed-loop system to good effect in late gestation.

The influence of lifestyle and behavioral factors during closed-loop is not well understood. Recent data have suggested that behavioral factors, including snacking, account for approximately one-third of the intraindividual variability in glucose levels during closed-loop insulin delivery (22). The frequency of premeal bolusing also is important, emphasizing the need for ongoing diabetes education and support with the closed-loop system (23). Others have commented that closed-loop insulin delivery may have unintended effects on dietary intake and proposed that education to optimize healthy eating patterns be incorporated into closed-loop training (24).

Previous qualitative research suggested that some patients may have unrealistic expectations, placing too much trust in the closed-loop system (15). This was echoed by pretrial comments from current participants, such as the following: "The way I see it is literally this app on this phone is literally going to take my brain away basically, which is happy days" (participant 4). During the qualitative interview, this participant commented that her motivation to participate was partly to avoid finger-stick testing: "I'm not the best with blood tests, but that's because I kind of more or less listen to the symptoms of highs and lows rather than doing a test, which is naughty, but that's the reason I wanted to go on the CLIP." (CLIP is the patient's abbreviation for Closed-Loop In Pregnancy.) Other authors have reported that the current closed-loop/artificial pancreas terminology may imply a more hands-off approach (25).

Although sensor use was reasonable for this patient population (~20 of 24 h), use of the closed-loop system was affected by technical problems that frequently required the device to be reset. The algorithm is adaptive, meaning that its performance improves for an individual over time. System errors requiring a reset meant that the algorithm returned to participant-naive parameters. Technical issues may have reduced participants' trust, which may also have contributed to them being tempted to override the algorithm's advice (26).

After 28 weeks' gestation, women achieved good overall glycemic control (71–73% time in target), which is comparable to our overnight home closed-loop study in women with well-controlled glucose levels (baseline HbA_{1c} 6.6%) who achieved 68–71% time in target (14). This is 10% higher than the control group in CONCEPTT (61% time in target) but comparable to the CONCEPTT CGM group (68% time in target) (5). The CONCEPTT participants had lower baseline HbA_{1c} levels and substantially more hypoglycemia, with 4% time <63.0 mg/dL and 3.5 hypoglycemia episodes/week. Taken together, these data suggest that closed-loop insulin delivery facilitates good day-to-day glucose control in a broad patient population and is effective for minimizing the risk of hypoglycemia. No episodes of severe hypoglycemia occurred during the current or previous closed-loop trials. We also found that despite frequent device hassles, 75% of women continued closed-loop therapy after delivery and for up to 6 weeks postpartum.

We cannot directly compare these pregnancy outcomes with the publicly reported data for all pregnancies from these sites (https://digital.nhs.uk/catalogue/PUB30109) because the participants in this study were 3 years older and had a 5-year longer duration of diabetes (19.4 vs. 14.0 years). Larger trials of longer-duration closed-loop insulin delivery are needed to understand the effect on maternal glucose control and infant health outcomes in routine care settings.

Meanwhile, obstetric and neonatal outcomes in T1D pregnancy remain suboptimal, suggesting that although the burden of maternal hypoglycemia can be minimized, excessive fetal exposure to maternal hyperglycemia persists. More research is needed to address the potentially modifiable dietary and snacking behaviors that contribute to postprandial hyperglycemia and are still challenging during closed-loop insulin delivery.

Strengths of this study include the randomized crossover design, which eliminates interindividual variability in insulin sensitivity, dietary intake, and exercise patterns and reduces the impact of gestation or the order of interventions. The analyses were performed as intention to treat regardless of compliance. Participants were recruited from three NHS sites and included women without diabetes technology experience and a wide range of glucose control. We did not use remote monitoring or restrict participants' dietary habits, exercise, or travel, rendering the study as real-world as possible.

We also acknowledge the limitations. The crossover design may not have been suitable for participants with variable lifestyles (e.g., night workers, overseas travelers).

The relatively short 4-week duration may have been insufficient for optimal closed-loop training, particularly for device-naive participants and those with less-advanced self-management skills. Although the prototype closed-loop system was portable and generally well received, it had frequent errors, which frustrated participants and reduced the time that closed-loop was operational. The SAP control group did not have the option of suspending insulin delivery during a low or predicted low glucose level.

In this cohort of pregnant women with T1D with a broad range of glucose control, closed-loop insulin delivery was as effective as SAP therapy but potentially safer because it reduced the extent and duration of hypoglycemia. More research is needed to improve glucose control in postprandial times and to develop closed-loop training programs to support optimal self-management behaviors, particularly for women who enter pregnancy with high HbA_{1c} levels. Larger trials of longer-duration closed-loop insulin delivery are required to determine proof of clinical efficacy in pregnancy and to establish whether future closed-loop systems may help to minimize neonatal complications in T1D pregnancy.

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Author Contributions. Z.A.S., M.E.W., G.R., E.M.S., K.B., C.F., R.H., and H.R.M. designed the study protocol. Z.A.S., S.H., L.K.O., and H.R.M. screened, enrolled, and consented participants and provided antenatal clinical care and telephone support throughout the trial. Z.A.S. and H.R.M. wrote the manuscript, which all authors critically reviewed. E.M.S. analyzed and interpreted sleep data. K.B. and C.F. performed the psychosocial assessments. R.H. designed the control algorithm. H.R.M. oversaw the conduct of the trial. Z.A.S., R.H., and H.R.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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