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Stewart, ZA, Wilinska, ME, Hartnell, S et al. (7 more authors) (2018) Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care, 41 (7). pp. 1391-1399. ISSN 0149-5992

https://doi.org/10.2337/dc17-2534

Day-and-night closed-loop in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial

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Abstract: 260, Text: 4095 (not including abstract, tables, figures, references, and online material)
Figures 2, Tables 4

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Abstract

Objective: Despite advances in technology, optimal glucose control remains elusive and neonatal complications 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.

Research Design and Methods: We recruited 16 pregnant women (mean age 32.8 (5.0) years, T1D duration 19.4 (10.2) years, HbA1c 8.0 (1.1)%, 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) separated by a washout. Afterwards, participants could continue using closed-loop up to 6-weeks post-partum. The primary endpoint was the proportion of time with glucose levels within target range (63-140mg/dl).

Results: The proportion of time with glucose levels within target was comparable during closed-loop and SAP (62.3% vs 60.1%; $CI_{95\%}$ -4.1 to 8.3; p=0.47). Mean glucose and time spent hyperglycemic >140mg/dl also did not differ (131.4 vs 131.4mg/dl; p=0.85 and 36.6 vs 36.1%; p=0.86). During closed-loop, there were fewer hypoglycemia episodes; median (range) 8 (1-17) vs 12.5 (1-53) over 28 days; p=0.04 and less time <63mg/dl (1.6 vs 2.7%; p=0.02). Hypoglycemia <50mg/dl (0.24 vs 0.47%; p=0.03) and low blood glucose index (1.0 vs 1.4; p=0.01) were lower. There was also less nocturnal hypoglycemia (23.00-07.00hr) during closed-loop (1.1 vs 2.7%; p=0.008) and a trend towards higher overnight time-in-target (67.7 vs 60.6%; p=0.06).

Conclusion: Closed-loop 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 in T1D pregnancy and impact on neonatal outcomes.

Introduction

Type 1 diabetes (T1D) in pregnancy is associated with 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 T1D pregnancy is to reduce fetal exposure to hyperglycemia without increasing maternal hypoglycemia. Recent evidence suggests that although continuous glucose monitoring (CGM) improves day-to-day glucose control, with approximately 1-hour/day less hyperglycemia in women using multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), optimal maternal glycemia was not achieved (5).

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

Hybrid closed-loop insulin delivery (artificial pancreas) systems provide automated glucose-responsive insulin delivery between meals and overnight, with manually triggered pre-meal doses (7). Closed-loop has been evaluated in children, adolescent, and adult populations under inpatient, outpatient, and home conditions and is associated with reduced exposure to hyperglycemia and hypoglycemia (8, 9). Short-term studies including non-pregnant adults with near-optimal glucose control (HbA1c<7.5%) suggest potential for reduced hypoglycemia (10). A recent systematic review and meta-analyses including 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 may be useful in T1D pregnancy, when glucose control targets are tighter and the burden of hypoglycemia burden 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, found a 15% increased time-in-target (75 vs 60%; p=0.002) between 23.00-07.00hr with closed-loop compared to SAP (14, 15). However, achieving optimal glucose control is substantially more challenging during the daytime when meals, snacks and exercise require manual pre-meal boluses with or without basal dose adjustment (16). As hybrid closed-loop systems adjust only basal insulin, the potential role of day-and-night closed-loop in T1D pregnancy is unknown. Our aim was to evaluate the safety, efficacy and longer-term feasibility of day-and-night closed-loop in pregnant women with T1D.

Methods

Study design

The trial was an open-label, randomized, two-period crossover study in pregnant women, assessing the safety, efficacy and longer-term feasibility of day-and-night closed-loop, as compared to SAP therapy, during T1D pregnancy.

After providing written informed consent, participants were trained on the use of the study CGM (FreeStyle Navigator 2, Abbott Diabetes Care, Alameda, CA, USA) and pump (DANA-R, Diabecare, Sooil, Seoul, South Korea) devices and practiced using them for 2-4 weeks before completing a device competency assessment to document that participants were competent using the study CGM and pump. Participants were

randomized to either 4-weeks of closed-loop (intervention) or 4-weeks of real-time CGM and CSII without closed-loop (SAP control). At the end of the first phase there was a 1-2 week washout, before participants crossed to the alternate phase. After the randomized trial, women could choose to resume their previous intensive insulin therapy or continue using the study devices (any combination of CGM, pump or closed-loop) throughout pregnancy and delivery and for up to 6 weeks post-partum. 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 programme, using permuted four-block schedule maintained in a secure database, ensuring that allocation was concealed from trial staff and participants. Participants were recruited from three UK National Health Service (NHS) antenatal clinics (Cambridge, Norwich, Ipswich). Women participated from within the home and antenatal clinic setting, with 24-hour support provided by the research team throughout.

Capillary glucose testing was recommended at least seven times daily with National Institute for Health and Clinical Excellence (NICE) glucose targets in both groups (pre-meal 63-99mg/dl, one-hour post meal <140mg/dl). There were no restrictions on exercise, meals or overseas travel and no remote monitoring. Participants had antenatal clinic visits every two weeks.

HbA1c outcome measurements were taken at randomization, the end of each crossover period, 28, 32 and 36 weeks gestation, and six weeks after delivery. They were analyzed at a central laboratory (Addenbrooke's Hospital, Cambridge, UK) using an International Federation of Clinical Chemistry and Laboratory Medicine

(IFCC) aligned method (TOSOH Bioscience G7 HPLC analyser; inter-assay CV 3.71% at HbA1c 5.41%; 1.7% at HbA1c 10.6%). Quality and quantity of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI), a sleep diary and by actigraphy (Actiwatch, Philips Respironics)(17). Participants completed questionnaires (Diabetes Technology Questionnaire and Hypoglycaemia Fear Survey) at baseline and at the end of each crossover (18, 19). Reportable adverse events included all serious adverse events other than pre-specified protocol exceptions.

Study participants

We recruited pregnant women who had T1D for at least one year before pregnancy. Women were aged between 18-45 years and had a singleton pregnancy with ultrasound-confirmed gestational age between 8-24 weeks. They had had intensive insulin treatment (either MDI or CSII), and a booking HbA1c level of ≥6.5 and ≤10% (≥48 and ≤86mmol/mol). Participants were required to speak and understand English and have email access.

Exclusion criteria included a physical or psychological disease likely to interfere with the conduct of the study, medications known to interfere with glucose metabolism, and 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 (15/EE/0278), with notification of no objection provided by the Medicines and Healthcare Products Regulatory Agency, UK (CI/2015/0042). All participants provided written informed consent. Details of the protocol and pre-

specified trial outcomes are available on the International Standard Randomised Controlled Trial Number register (ISRCTN 83316328).

Closed-loop system

The closed-loop system (Florence D2A, University of Cambridge, Cambridge, UK) used CGM glucose measurements to automatically adjust insulin rates. Real-time glucose readings were transmitted using Bluetooth via a purpose-built translator to an android mobile phone (Samsung Galaxy S4, Samsung, South Korea), which housed the algorithm. The control algorithm (University of Cambridge, version 0.3.41p) aimed for interstitial glucose levels of 104.4-131.4mg/dl, adjusting for fasting and post-meal conditions and for accuracy of glucose prediction. It 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 minutes, the insulin dose was communicated via 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 including Medtronic (Northridge, California, USA) and Animas (West Chester, Pennsylvania, USA).

Pre-meal insulin boluses were given manually, 15-30 minutes before eating, using the pump's bolus calculator. To initialize closed-loop, participant's weight and total daily insulin dose were entered manually, with insulin pump settings automatically transferred using Bluetooth. Safety rules limited maximum insulin dose and suspended insulin delivery when glucose levels were falling rapidly and/or <77.4mg/dl. Capillary glucose calibration tests were advised twice daily (before

breakfast and evening meal). Recalibration of CGM was recommended if sensor and capillary glucose levels differed by ≥54mg/dl.

At the start of closed-loop, participants had a device training session (30-60 minutes). This included instructions for starting and stopping closed-loop and troubleshooting for technical issues. During the randomized trial and follow-up, participants were advised to use closed-loop continuously. To maintain device connectivity, participants had to be within approximately 30 meters of the devices. There were no changes to announce for antenatal corticosteroids, labor, or delivery but the non-pregnant glucose targets (70-180mg/dl) were applied immediately post-partum. Participants had access to a 24-hour phone line staffed by the research team.

Study endpoints

Safety endpoints included nocturnal (23:00-07:00hr) and/or severe hypoglycemia episodes (defined as requiring third party assistance and/or capillary glucose < 50mg/dl associated with clinical symptoms) and other adverse events.

The primary efficacy endpoint was the percentage of time spent within the T1D pregnancy target range (63-140mg/dl), as measured by CGM during the 4-week intervention periods. Pre-specified secondary glycemic outcomes, derived from CGM measures, included mean glucose, time >140 and >180mg/dl (to quantify fetal hyperglycemic exposure), time <63 and <50mg/dl (to quantify maternal hypoglycemia), maternal hypoglycemia episodes (<63mg/dl for ≥20 minutes duration), low blood glucose index (LBGI) to quantify hypoglycemia duration and extent (20), and standard deviation (SD) to quantify glucose variability. Additional

outcomes included central laboratory HbA1c, time in non-pregnant target range (70-180mg/dl), CGM compliance, total insulin dose, questionnaires and measures of sleep.

The longer-term feasibility of day-and-night closed-loop (from the end of the randomized trial until delivery) was assessed by CGM measures during pre-specified intervals (28-32, 32-36 and from 36 weeks until delivery). The glucose target range was adjusted to 70-180mg/dl (non-pregnant), during the assessment period from after delivery until up to 6-weeks post-partum.

Statistical analysis

Previous study participants using SAP therapy spent 61.7 (24.9)% time-in-target (16, 21). To detect a 30% relative increase (from 62% to 80%), we estimated that a sample size of 16 participants was needed to achieve 80% power and an alpha level of 0.05 (two-tailed). The standard deviation 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, Cambridge UK) and statistical analyses 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; the study arm as a fixed effect; and study participant and 4-week block as nested random effects.

Role of the funding source

The funders had no role in the trial design, data collection, data analysis, data interpretation, or the decision to publish. Abbott Diabetes Care (Alameda, California,

USA) provided discounted CGM devices and consumables. The National Institute for Health Research and Abbott Diabetes Care reviewed the manuscript prior to submission but did not play a role in manuscript preparation or revision. The corresponding author (HRM) oversaw the conduct of the trial, had full access to all the data and takes full responsibility for the decision to submit for publication.

Results

Study participants

Nineteen participants were recruited to the study (Figure 1). Of these, two withdrew prior to randomization (one disliked study pump, one experienced mental health deterioration) and one withdrew due to 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, with equal numbers of pump and MDI users and nine (56%) participants with suboptimal HbA1c (Table 1).

Randomized crossover trial outcomes

There was no difference in the primary outcome, percentage of time in the target glucose range (63-140mg/dl), during closed-loop and SAP (62.3% vs 60.1%; absolute difference 2.1%, $CI_{95\%}$ -4.1 to 8.3; p=0.47, Table 2). Likewise, mean glucose and time spent hyperglycemic >140mg/dl did not differ between closed-loop and SAP (131.4 vs 131.4mg/dl; p=0.85 and 36.6 vs 36.1%; p=0.86). During the 4-weeks of closed-loop, there were fewer episodes of maternal hypoglycemia;

median (range) 8 (1-17) vs 12.5 (1-53); p=0.04 and less time spent below 63mg/dl (1.6 vs 2.7%; $CI_{95\%}$ -0.2 to -2.1; p=0.02). Time below 50mg/dL (0.24 vs 0.47%; $CI_{95\%}$ -0.02 to -0.5; p=0.03) and low blood glucose index (1.0 vs 1.4; $CI_{95\%}$ -0.7 to -0.1; p=0.01) were lower during closed-loop.

There was less overnight time (23.00-07.00h) below 63mg/dl during closed-loop (1.1 vs 2.7%; $CI_{95\%}$ -2.8 to -0.4; p=0.008). The overnight time-in-target was also higher during closed-loop but this difference did not reach statistical significance (67.7 vs 60.6%; $CI_{95\%}$ -0.8 to 15.2; p=0.06; Supplemental Table S1) .

There were no episodes of severe hypoglycemia. The mean (SD) HbA1c was 6.6% (2.8) (48.5mmol/mol [7.5]), 6.4% (2.7) (46.3mmol/mol [5.6]) and 6.3% (2.7) (45.9mmol/mol [5.5]), at baseline, end of closed-loop and end of SAP, respectively. There was no difference in HbA1c between baseline and the end of each phase (p= 0.15 and p= 0.14 for closed-loop and SAP respectively), and no difference in HbA1c during closed-loop and SAP (p=0.67). There were no differences in total insulin doses, although basal insulin delivery was, as expected, more variable during closed-loop (SD 0.1 vs 0.8; p<0.0001; Supplemental Table S2).

The quality and quantity of sleep were comparable, with a sleep duration of 7.5 (0.8) during closed-loop and 7.1 (1.2) hours during SAP (p=0.22). There were no differences in the patient-reported questionnaires. Most participants (>80% at the end of both phases) reported less fear of nocturnal hypoglycemia, although over a third experienced ongoing worry or fear about low blood sugars during sleep.

There were no reportable serious adverse events but there were frequent device deficiencies, most frequently, involving the closed-loop mobile phone (47%) and

CGM (30%) devices with fewer concerns regarding the insulin pump (13%) and device downloads (10%; Supplemental Table S3).

Longer-term antenatal feasibility

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

Post-partum closed-loop feasibility

After delivery, 12 women chose to continue using closed-loop. They maintained safe glucose control, with 77.1% time-in-target (70-180mg/dl) and minimal hypoglycemia (2.3% < 70mg/dl) during the first 6-weeks post-partum (Table 3). Sensor wear was variable after delivery, with a median of 16.5 hours/day. Where post-partum sensor wear was low, it was generally the case that the participant used CGM for the lifespan of a sensor, with gaps between the expiry of one sensor and insertion of a new one (Supplemental Table S4).

Obstetric and neonatal outcomes

Participants delivered at a median (interquartile range) gestation of 36.9 (36.1 - 37.8) weeks gestation. Thirteen were delivered by caesarean section, seven of which occurred prior to the onset of labor. Two participants developed pre-eclampsia. One participant had a placental abruption. The median (interquartile range) neonatal

birthweight was 3575g (3073-3745). Seven (44%) were LGA ≥90th centile, with five ≥ 97th centile. One neonate, born to a mother with excellent glucose control (participant 7), was small-for-gestational age (birthweight 2880g), but was healthy and without complications. Eleven (69%) infants were admitted to NICU, with seven (44%) treated for hypoglycemia (Supplemental Table S5, S6).

Two infants had congenital anomalies. One had a neural tube defect (lumbar/sacral lipomyelomeningocele) detected post-partum. This mother had an unplanned pregnancy (booking HbA1c 8.1%), switched from MDI to closed-loop with good effect and maintained excellent glucose control throughout pregnancy (participant 2). Another infant had severe unilateral hydronephrosis (10mm renal pelviceal dilatation detected at 20 weeks gestation). This participant (booking HbA1c 9.7%), conceived spontaneously after four unsuccessful cycles of IVF, also switched from MDI to closed-loop, with a striking fall in HbA1c (5.0%) despite modest time-in-target (56%) in late pregnancy (Supplemental Table S5, S6).

Inter-individual variability

The individual participant data highlights variability in women's glycemic responses to closed-loop (Figure 2). This does not appear related to previous technology use as glycemic control was comparable in participants who used CSII or MDI at enrolment (Supplemental Table S7). Five participants (31%) spent less time in target and had higher mean glucose levels during closed-loop. These included two CSII (participants 3, 5) and three MDI users (participants 4, 6, 13) had ≥10% lower time-in-target during the closed-loop crossover, although they all continued to use closed-loop, with higher time-in-target, in later pregnancy.

Post hoc analyses suggested that participants with lower booking HbA1c levels (≤7.5%) had higher time-in-target both during closed-loop and SAP phases, compared to those with HbA1c>7.5% (Table 4). This pattern persisted throughout pregnancy, including after 36 weeks, when participants with lower HbA1c in early pregnancy maintained excellent glucose control (mean glucose 115mg/dl, 78% equivalent to 18.7 hours/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, (126mg/dl, 69% in-target or 16.6 hours/day).

Discussion

We found that day-and-night closed-loop was 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, with no between-group differences in time-in-target, mean glucose, or HbA1c levels. There was a reduction in frequency of maternal hypoglycemic events and reduced exposure both to overall and to nocturnal hypoglycemia during closed-loop.

The current study is part of a phased programme of developing and evaluating closed-loop in pregnancy. The first non-randomized, 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, over 24 hours in the clinical research facility (16). The third was the first home study of overnight closed-loop with the same sample size (n=16), randomized crossover design, same 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 of pregnancy, closed-loop was associated with a 12.6% increased time-in-target range where the comparator (SAP in 21/22 single hormone closed-loop studies), spent 58% time (13.3 hours/day) in the wider glucose target range of 70-180mg/dl (11). In the current study, where both groups had over 60% time-in-target range (63-140mg/dl for T1D pregnancy), no further improvement was obtained. Our previous study of overnight closed-loop in pregnancy (14), also found that compared to SAP, closed-loop was associated with a 15% higher time-in target (75 vs 60%; $p<0.002$). In our current study, women using SAP achieved comparable overnight glucose control, but the impact of closed-loop effect was less, with a 7% non-significant increase (68 vs 61%; $p=0.06$).

There are several potential explanations for our findings. Firstly, the level of glucose control achieved with SAP (60% in 70-140mg/dl, and 82.5% in 70-180mg/dl range), in pregnancy is considerably higher than in previous studies outside pregnancy (8, 9, 11). The glucose control achieved with SAP in our study was comparable or higher than that achieved with closed-loop previously (8, 9), including in well-controlled adults (HbA1c <7.5%), thereby minimising the potential for further improvement (10). The role of closed-loop, in well-controlled adults, may be to reduce the burden of hypoglycemia without deterioration in glucose control.

Secondly, 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 suggest that even small differences, a 7% increase time-in-target and 5% reduction

in hyperglycemia in CONCEPTT, are associated with substantial (approximately 50%) reductions in neonatal complications (5). The current study was underpowered to detect small differences.

Thirdly, we consciously enrolled a broad patient population for this study, including women with variable levels of technology experience, diabetes education and glycemic control. The majority were technology naïve with over 80% sensor naïve and 50% pump naïve at enrolment. Over half had suboptimal booking HbA1c levels, defined as HbA1c>7.5% at the first antenatal visit. Among the five women with lower time-in-target during closed-loop, one cycled 30-60mins twice daily and struggled to avoid post-exercise hypoglycemia (participant 3), while another who worked as an events planner, had more night shifts during closed-loop (participant 4). Three women (participants 4, 6, 13) were frequent non-attenders at antenatal clinics and had minimal contact with the research team. All three used closed-loop to good effect in late gestation.

The influence of lifestyle and behavioural factors during closed-loop is not well understood. Recent data suggest that behavioural factors, including snacking, account for approximately one third of the intra-individual variability in glucose levels during closed-loop (22). The frequency of pre-meal bolusing is also important, emphasising the need for ongoing diabetes education and support with closed-loop (23). Others have commented that closed-loop may have unintended impacts on dietary intake, and proposed that education to optimise healthy eating patterns be incorporated into closed-loop training (24).

Previous qualitative research suggests that some participants may have unrealistic expectations placing too much trust in closed-loop (15). This was echoed by pre-trial

comments from current participants; “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, she 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 tes*t, which is naughty, but that’s the reason I wanted to go* on the CLIP”. Other authors have reported that the current “closed-loop/artificial pancreas” terminology, may imply a more "hands-off" approach (25).

While sensor use was reasonable for this patient populati (approximately 20 of 24 hours), use of closed-loop was affected by technical problems that frequently required closed-loop to be reset. The algorithm is adaptive, meaning that its performance improves for an individual over time. System errors requiring that the system be reset meant that the algorithm returned to participant-naïve parameters. Technical issues may have reduced womens trust, which may also have contributed to them being tempted to override the algorithm advice (26).

After 28 weeks gestation, women achieved good overall glycemic control (71-73% time-in-target). This is comparable to our overnight home closed-loop study, in well-controlled women (baseline HbA1c 6.6%), who achieved 68-71% time-in-target (14). It 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 HbA1c 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 facilitates good day-to-day glucose control in a broad patient population, and is effective for minimising risk of hypoglycemia. There were no episodes of severe hypoglycemia during the current or

previous closed-loop trials. We also found that despite frequent device hassles, 75% of women continued closed-loop after delivery, and for up to 6-weeks post-partum.

The obstetric and neonatal outcomes remain suboptimal, suggesting that while the burden of maternal hypoglycemia can be minimised, excessive fetal exposure to maternal hyperglycemia persists. More research is needed to address the potentially modifiable dietary and snacking behaviours that contribute to post-prandial hyperglycemia and are still challenging during closed-loop.

Strengths of this study include the randomized crossover design, eliminating inter-individual variability in insulin sensitivity, dietary intake, and exercise patterns and reducing 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, including women without diabetes technology experience and with 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 travel). The relatively short 4-week duration may have been insufficient for optimal closed-loop training particularly for device naïve participants and those with less advanced self-management skills. While the prototype closed-loop system was portable and generally well received, it had frequent errors. This 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 low or predicted low glucose level.

In this cohort of pregnant women with type 1 diabetes, with a broad range of glucose control, closed-loop was as effective as SAP therapy, but potentially safer, because closed-loop reduced the extent and duration of hypoglycemia. More research is needed to improve glucose control in postprandial times and to develop closed-loop training programmes to support optimal self-management behaviours, particularly for women who enter pregnancy with higher HbA1c. Larger trials of longer duration closed-loop are required to determine proof of clinical efficacy of in pregnancy and to establish whether future closed-loop systems may help to minimise neonatal complications in T1D pregnancy.

Funding: The trial is funded by the National Institute for Health Research (HRM Career Development Fellowship, CDF-2013-06-035), Gates Cambridge Trust PhD fellowship (ZAS), Jean Hailes for Women's Health (ZAS); and a grant from the NIHR Cambridge Biomedical Research Centre (RH). Abbott Diabetes Care supplied discounted CGM devices, sensors, and details of communication protocol to facilitate real-time connectivity. HRM conducts independent research supported by the National Institute for Health Research (CDF-2013-06-035). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the UK Department of Health.

Acknowledgements

The authors would like to thank all the pregnant women with type 1 diabetes who participated, along with their partners and families. We also acknowledge the invaluable support from the diabetes antenatal care teams in Cambridge, Norwich and Ipswich.

Contributors: ZAS, MEW, GR, EMS, KB, CF, RH, HRM designed the study protocol. ZAS, SH, LON, HRM screened, enrolled and consented participants, provided antenatal clinical care and telephone support throughout the trial. EMS analysed and interpretated sleep data. CF and KB performed the psychosocial assessments. RH designed the control algorithm. ZAS and HRM wrote the manuscript, which all authors critically reviewed. ZAS, RH and HRM had full access to all the data and take responsibility for the integrity of the data, and accuracy of the analyses.

Competing Interests: HRM serves on the Medtronic European Scientific Advisory Board. RH received speaker honoraria from Eli Lilly and Novo Nordisk and license

fees from B Braun and Medtronic; is on advisory panels for Eli Lilly and Novo Nordisk; has served as a consultant to B Braun; and reports patents and patent applications. MEW received license fees from Becton Dickinson, has served as a consultant to Beckton Dickinson, and reports patents and patent applications.

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Table 1: Baseline characteristics of trial participants

Baseline characteristics (N=16)	Number (%)	Mean (SD)
Age (years)		32.8 (5.0)
BMI (kg/m^2)		26.6 (4.4)
Booking HbA1c[†] (%)		8.0 (1.1)
Booking HbA1c (mmol/mol)		63.7 (12.1)
Booking HbA1c >7.5% (58mmol/mol)	9 (56%)	
Duration of diabetes (years)		19.4 (10.2)
Insulin pump use prior to study	8 (50)	
CGM use prior to 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 HbA1c is the measurement taken at the first antenatal clinic visit following confirmed pregnancy

* Weeks gestation at randomization. Randomization was performed after recruitment and at least 2 to 4 weeks of device training when insulin regimens were optimised and participants were competent using the study pump and CGM devices.

± None of the 3 participants had used CGM in the 6 months prior to enrollment in the study or as part of their regular diabetes management. Two had used real-time CGM (C24_03_06, C24_01_12) and one Freestyle Libre (C24_02_15).

‡6 participants had experienced previous pregnancy losses (6 miscarriages and 1 stillbirth), 2 women had had termination of pregnancy for major malformation. 2 women had a history of hypertensive disorders of pregnancy.

Table 2: Glycemic outcomes of trial participants

	Sensor-augmented pump	Closed-loop	Absolute difference ($CI_{95\%}$)	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 outcomes				
Mean CGM glucose (mg/dl)	131.4	131.4	0 (-0.3 to 0.4)	0.85
Time > 140mg/dl or 7.8mmol/L (%)	36.6	36.1	-0.6 (-7.4 to 6.3)	0.86
Time >180mg/dl or 10mmol/L (%)	14.8	14.6	-0.1 (-4.2 to 4.0).	0.94
Time <63mg/dl or 3.5mmol/L (%)	**2.7**	**1.6**	**-1.1 (-0.2 to -2.1)**	**0.02**
Time 50mg/dl or < 2.8mmol/L (%)	**0.5**	**0.2**	**-0.2 (-0.0 to -0.5)**	**0.03**
Number of hypoglycemic events over 28 days	**12.5 (1-53)**	**8 (1-17)**		**0.04**
Low blood glucose index (LGBI) [±]	**1.4**	**1.0**	**-0.4 (-0.7 to -0.1)**	**0.01**
Standard deviation 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 (hours/day)	20.3	20.2		

The values reported are derived from linear mixed effects models except for number of hypoglycemic events which are median (range) and defined as sensor glucose values <63mg/dl for ≥20 minutes.

* The primary efficacy endpoint was the percentage of time that glucose was in the T1D pregnancy target range of 63-140mg/dl (3.5-7.8mmol/L), as recorded by CGM during each 4-week study phase.

[±]The low blood glucose index assessed the duration and extent of hypoglycemia.

Table 3: Glycemic control during the antenatal and post-partum closed-loop feasibility phases[±].

	Antenatal feasibility			Postnatal feasibility
	28-32 weeks	**32-36 weeks**	**>36 weeks**	**0-6 weeks**
	n=8	**n=16**	**n=9**	**n=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 (hours/day)	22.4 (11.3, 23.2)	19.9 (15.1, 23.0)	N/A	16.5 (11.6, 19.2)

Data are median (interquartile range)

[±]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 post-partum.

* The glucose target range was 63-140mg/dl (3.5-7.8mmol/L) during pregnancy and 70-180mg/dl (3.9-10.0mmol/L) after delivery.

Table 4: Glycemic control during the randomized crossover trial and antenatal closed-loop feasibility phase in participants with HbA1c levels≤7.5% or >7.5% (58mmol/mol) at their first antenatal clinic visit.

	Booking HbA1c ≤7.5% (n=7)†						**Booking HbA1c >7.5% (n=9)†**					
	Sensor-augmented pump	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**	**Sensor-augmented pump**	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**
% Time in target (63-140mg/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 below 63mg/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*

†The booking HbA1c is the measurement taken at the first antenatal clinic visit following confirmed pregnancy

*Indicates significant difference between participants with HbA1c ≤7.5% compared with booking HbA1c >7.5% ($p<0.05$)