Automated closed-loop insulin delivery for the management of type 1 diabetes during pregnancy: the AiDAPT RCT

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Scientific summary

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Scientific summary

Background

There are over 2000 pregnancies annually in women with type 1 diabetes. These pregnancies are complicated by high and increasing rates of preterm births, large for gestational age birthweight babies and neonatal care unit admissions. Obstetric and neonatal complications are lowest in mothers who achieve target glucose levels, which requires unrelenting attention to diabetes self-management and insulin dose adjustment throughout pregnancy.

Despite improvements in diabetes technology, including continuous glucose monitoring (CGM) and insulin pumps, most pregnant women with type 1 diabetes cannot achieve or maintain the pregnancy glucose targets. National audit data confirm that only 15% of women enter pregnancy with the recommended glycated haemoglobin A1c (HbA1c) target of < 48 mmol/mol (6.5%). Using the daily glucose targets of 3.5–7.8 mmol/l, as recommended by the National Institute for Health and Care Excellence (NICE) and international consensus guidelines for CGM measures, women with type 1 diabetes currently spend 12 hours per day or 50% time in range (TIR) in early pregnancy, increasing to 60–70% in the final stages of pregnancy. Thus, one in two babies are admitted to neonatal care units with diabetes-related complications.

Hybrid closed-loop systems provide automated glucose-responsive insulin delivery between meals and overnight but require manual user-initiated pre-meal insulin doses. Hybrid closed-loop therapy is associated with improved glucose levels in randomised controlled trials and is now increasingly used in real-world clinical settings. While preliminary studies suggest potential benefits for maternal well-being and glycaemic outcomes, the role of hybrid closed-loop during type 1 diabetes pregnancy has not been established. We hypothesised that hybrid closed-loop, used from 16 weeks' gestation, would improve maternal glucose levels throughout pregnancy.

Objectives

To examine the clinical efficacy of using hybrid closed-loop, compared to standard insulin delivery, on maternal glucose levels during type 1 diabetes pregnancy. We also sought to explore women's and healthcare professionals' experiences of using hybrid closed-loop during pregnancy.

Methods

In a multicentre, open-label, randomised controlled trial, we randomised 124 pregnant women with type 1 diabetes using standard insulin therapy, to CGM with or without hybrid closed-loop. Participants were recruited from nine antenatal hospital clinics in England, Scotland and Northern Ireland. Those with an ultrasound-confirmed pregnancy and HbA1c of 48 to ≤ 86 mmol/mol (6.5 to ≤ 10.0%) at ≤ 13 weeks and 6 days' gestation were eligible for recruitment. At least 96 hours (including 24 hours overnight) of baseline CGM glucose values were required before randomisation, which was allocated on a 1 : 1 basis and stratified by clinical site.

Control-arm participants used CGM (Dexcom G6 CGM; Dexcom, Inc., San Diego, CA, USA) alongside standard care insulin delivery, which was either multiple daily injections or insulin pump therapy. Training (inperson or virtual) was provided by local teams on CGM sensor insertion, CGM data interpretation, dietary advice and insulin dose adjustment.

The hybrid closed-loop system has three components: an app hosted on an Android smartphone which runs the algorithm (CamAPS® FX, CamDiab Ltd, Cambridge, UK) that adjusts insulin delivery via an insulin pump (Dana Diabecare RS, Advanced Therapeutics UK Ltd., Warwick, UK) according to continuous glucose measurements (Dexcom G6). A training session (inperson or virtual) covering using the closed-loop study devices, alarms and troubleshooting was provided by the study research educator or local care team. This included instruction on pre-meal insulin doses, personal glucose targets and specific (boost or ease-off) features to intensify or reduce insulin delivery. Personal glucose targets were user-specified but recommended targets were 5.5 mmol/l in early pregnancy, and 4.5–5.0 mmol/l from 16 to 20 weeks' gestation onward.

Study visits were scheduled at 4-weekly intervals from 16 weeks until delivery. Participants in both arms received standard antenatal diabetes and obstetric care (usually in conjunction with study visits) from their local teams. Participants in both groups were given standard glucose targets (pre-meal 3.5–5.5 mmol/l and 1 hour post meal < 7.8 mmol/l) and encouraged to administer pre-meal insulin at least 10–15 minutes before eating. Capillary ketone measurement was advised during illness or hyperglycaemia (> 10 mmol/l).

The primary outcome was the percentage of time spent with CGM glucose levels between 3.5 and 7.8 mmol/l between 16 weeks' gestation and delivery. Safety outcomes included the number and severity of diabetic ketoacidosis (DKA), severe hypoglycaemia (SH) and adverse device events.

Patient-reported outcomes were reported at around 34–36 weeks' gestation using the following validated questionnaires: Insulin Delivery Systems: Perspectives, Ideas, Reflections and Expectations (INSPIRE); EuroQol-5 Dimensions health-related quality-of-life questionnaire (EQ-5D), Diabetes Distress Scale (DDS), hypoglycaemia fear survey II (HFS – worry scale only) and Pittsburgh Sleep Quality Index (PSQI).

Maternal and neonatal outcomes were documented at hospital discharge following delivery.

Protocol amendments implemented during the COVID-19 pandemic allowed participants the option to continue using CGM with standard or closed-loop insulin delivery as per their initial randomisation for up to 6 months post partum. Outcomes for those who participated in the observational post-partum extension study will be reported separately. Details of the clinical study protocol are published.

Primary outcome analysis was by intention-to-treat using a linear mixed-effects regression model adjusted for baseline CGM TIR, insulin delivery and clinical site. Missing primary end-point data were handled using multiple imputation (Rubins and direct likelihood methods) with all randomised participants included. For secondary outcomes, analyses were similar to the primary analysis, without imputation. False discovery rate (FDR)-adjusted *p*-values were calculated for selected secondary outcomes (overall, overnight, and by-trimester sensor glucose metrics, HbA1c, insulin doses, subgroup analyses, questionnaires) using Benjamini–Hochberg methods. For attainment of sensor glucose targets, a mixed-effects logistic regression model was fitted adjusting for baseline TIR, insulin delivery and clinical site as a random effect. All *p*-values are two-tailed. Analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA; SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries.® indicates USA registration).

Results

Participants

Between September 2019 and May 2022, 334 participants were assessed for eligibility, with 126 enrolled and 124 randomised: 61 to the closed-loop intervention group and 63 to the standard care

control group. Participants were from nine NHS maternity clinics and spanned a range of maternal age, body weight and glycaemic categories. Almost all (98%) were using CGM and approximately half were using insulin pump therapy at enrolment. Participants in the closed-loop group had more previous pregnancies, while those in the standard care group reported more previous DKA events.

Two participants switched from their randomised allocation group: one intervention participant for whom lockdown restrictions prevented closed-loop training and one standard care participant who procured closed-loop (CamAPS FX) outside of the trial. Seven participants in each group discontinued their allocated treatment.

Despite the impact of the COVID-19 pandemic, the proportion of completed study visits was high (approximately 95%). Participants in the standard care group had more additional clinic visits (1.5 vs. 1.1) and more unscheduled contacts (9.6 vs. 6.1), mostly for pregnancy and diabetes-related reasons. The frequency of sensor use was consistently high: median 97% across both treatment groups. The frequency of closed-loop use was high (median 96%) and remained > 95% throughout pregnancy.

Primary efficacy end point

The mean (± standard deviation) percentage of time that maternal glucose levels were within the pregnancy target range increased from 47.8 ± 16.4% to 68.2 ± 10.5% in the closed-loop group and from 44.5 ± 14.4% to 55.6 ± 12.5% in the control group [mean-adjusted difference 10.5 percentage points, 95% confidence interval (CI) 7.0 to 14.0 percentage points; $p < 0.001$].

Adjustment for potential confounding variables, including previous pregnancies and DKA episodes, did not change the treatment difference. There were no variations in the treatment effect between trial sites and no differential effects across maternal age, HbA1c or insulin delivery categories. The large treatment difference was consistent between intention-to-treat and per-protocol analyses and using multiple imputation methods.

Secondary glycaemic outcomes

Participants randomised to closed-loop spent less time with glucose levels above target range (mean difference −10.2%, 95% CI −13.8% to −6.6%; $p < 0.001$). This was accompanied by decreased hyperglycaemia across milder (> 6.7 mmol/l) and more pronounced (> 10.0 mmol/l) categories, as well as lower mean glucose and lower HbA1c (mean difference −0.31%, 95% CI −0.50% to −0.12%; $p < 0.002$). These changes are notable since participants in both groups spent approximately 70% of time in the near-optimal glucose range of 3.5–10.0 mmol/l at enrolment. Furthermore, in those who started closed-loop therapy during the first trimester, a 5% higher TIR was observed by the end of 12 weeks' gestation.

The effects of the intervention during the overnight period (23.00–07.00) closely followed the 24-hour results (12.3% higher TIR, 95% CI 8.3% to 16.2%; $p < 0.001$). This was accompanied by less nocturnal hypoglycaemia and fewer nocturnal hypoglycaemic events. Attainment of the sensor glucose target of > 70% time (16 hours 48 minutes) within the pregnancy-specific range was achieved by 28 (47%) closed-loop and 7 (11%) standard care participants. Attainment of the sensor glucose target of < 25% time (6 hours) spent hyperglycaemic was also achieved by more closed-loop participants: 22 (37%) closed-loop compared to 7 (11%) standard care.

Maternal glucose improvements were achieved without additional hypoglycaemia or total daily insulin dose. There were no between-group differences in patient-reported outcomes.

Maternal and neonatal outcomes

There was one shoulder dystocia in the closed-loop group. There were four serious birth injuries [hypoxic ischaemic encephalopathy (HIE)], including one neonatal death attributed to HIE in the standard care group. We observed less new-onset hypertension and more repeat caesarean sections in the closed-loop group, likely related to their previous pregnancies. We also observed 3.7 kg less

gestational weight gain in the closed-loop group. Babies of mothers in the closed-loop group were delivered 4.5 days earlier, without differences in preterm births, birthweight, neonatal complications or neonatal care admissions.

Safety outcomes

There were six SH events in the closed-loop group and five in standard care. There was one DKA in each group. One participant with severe hyperemesis experienced 20 non-acidotic ketosis events. She did not use closed-loop at any time between 16 weeks' gestation and delivery but during this time contributed to more ketosis and serious adverse events in the closed-loop group. The rate of adverse device events for the closed-loop system was 24.3 per 100 person-years.

Conclusions

We found that the percentage of time that glucose levels were within the pregnancy-specific target range of 3.5–7.8 mmol/l from 16 weeks' gestation until delivery was 10.5 percentage points higher (an additional 2.5 hours per day) in participants who used closed-loop, compared to those who used CGM alongside their usual insulin delivery method. The TIR benefits were achieved by reducing maternal hyperglycaemia across mild to moderately severe thresholds. These observations were accompanied by striking nocturnal improvements, including higher TIR (12.3 percentage points), lower time below range and fewer night-time hypoglycaemic events. Improvements in maternal glucose outcomes were consistent across baseline maternal characteristics, HbA1c categories, clinical sites and pre-trial insulin delivery method (insulin pump or injections). Furthermore, there was 3.7 kg less gestational weight gain and no increase in maternal insulin doses. A clinically relevant five percentage point increased TIR was apparent by the end of the first trimester, suggesting that the benefits occurred soon after closed-loop initiation (approximately 12 weeks' gestation), which is crucially important for women and clinicians considering therapeutic changes during early pregnancy.

A beneficial effect of closed-loop therapy was also seen in decreased mean glucose and HbA1c levels. The incidence of hypoglycaemia was low at baseline and, apart from night-time reductions, did not differ between the study groups. The trial was initiated prior to and continued during the COVID-19 pandemic, which particularly impacted pregnant women and necessitated rapid implementation of virtual training and trial visit procedures. Nonetheless, closed-loop usage was high (> 95%) throughout pregnancy, and without apparent safety problems, including among those new to insulin pump therapy. Indeed, participants who continued standard care had more clinic visits and more unscheduled contacts, suggesting that beyond initial training, closed-loop use did not require additional healthcare professional input.

Recent trials have demonstrated the benefits of CamAPS FX to those with newly diagnosed type 1 diabetes and young children, and these results further extend the evidence for closed-loop therapy to pregnant women. During pregnancy, women in the closed-loop group increased the percentage of time with near-target glucose levels (3.5–10.0 mmol/l) from 71 to 87%. This is, to the best of our knowledge, the tightest glycaemic control yet achieved through use of closed-loop therapy. Alongside women's motivation to minimise pregnancy complications, closed-loop use facilitated attainment of 70% time in pregnancy-specific target range throughout gestation. This suggests that tighter glycaemic control could also be feasible outside of pregnancy, when clinically warranted. Given the rapid increases in TIR observed within 1 week of therapy initiation in this trial, and within 1 day in a recent trial, we speculate that further benefits may be obtained from starting closed-loop before pregnancy, or as soon as possible, after pregnancy is confirmed.

The current trial participants gained an additional 10% TIR above and beyond the 10% increment achieved by CGM and standard insulin therapy across pregnancy. Previous studies demonstrated that every 5% increased TIR is associated with improved obstetric and neonatal outcomes. Our trial was not

powered for pregnancy outcomes, but we infer that this additional 10% time in the pregnancy target range would be expected to have additional health benefits for mothers and their babies.

The strengths of our trial include its parallel-group, randomised controlled design, generalisability of our patient population, including those naive to insulin pump therapy and a large proportion who initiated therapy during the first trimester, and a flexible pragmatic trial protocol that facilitated virtual or in-person visits. There was no evidence of increased clinical contacts, frequently observed in investigational device trials. This trial had certain limitations. We did not undertake a health economic evaluation and the current sample size did not provide definitive data on maternal and neonatal health outcomes. Furthermore, our data are applicable only to the CamAPS FX closed-loop system and cannot be extrapolated to systems with higher glucose targets.

Closed-loop therapy was effective in type 1 diabetes pregnancy, safely accommodating the marked gestational changes in insulin doses across a range of maternal body weight and glycaemic categories. It gave additional clinical advantage above and beyond that which can be achieved by CGM and standard insulin therapy, supporting NICE guideline recommendations that hybrid closed-loop therapy should be offered to all pregnant women with type 1 diabetes.

Trial registration

This trial is registered as ISRCTN56898625.

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