ORIGINAL ARTICLE

Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes

Tara T.M. Lee, M.B., B.S., Corinne Collett, B.Sc., Simon Bergford, M.S., Sara Hartnell, B.Sc., Eleanor M. Scott, M.D., Robert S. Lindsay, Ph.D., Katharine F. Hunt, M.D., David R. McCance, M.D., Katharine Barnard-Kelly, Ph.D., David Rankin, Ph.D., Julia Lawton, Ph.D., Rebecca M. Reynolds, Ph.D., Emma Flanagan, Ph.D., Matthew Hammond, M.Sc., Lee Shepstone, Ph.D., Malgorzata E. Wilinska, Ph.D., Judy Sibayan, M.P.H., Craig Kollman, Ph.D., Roy Beck, Ph.D., Roman Hovorka, Ph.D., and Helen R. Murphy, M.D., for the AiDAPT Collaborative Group*

ABSTRACT

BACKGROUND

Hybrid closed-loop insulin therapy has shown promise for management of type 1 diabetes during pregnancy; however, its efficacy is unclear.

METHODS

In this multicenter, controlled trial, we randomly assigned pregnant women with type 1 diabetes and a glycated hemoglobin level of at least 6.5% at nine sites in the United Kingdom to receive standard insulin therapy or hybrid closed-loop therapy, with both groups using continuous glucose monitoring. The primary outcome was the percentage of time in the pregnancy-specific target glucose range (63 to 140 mg per deciliter [3.5 to 7.8 mmol per liter]) as measured by continuous glucose monitoring from 16 weeks' gestation until delivery. Analyses were performed according to the intention-to-treat principle. Secondary outcomes included were the percentage of time spent in a hyperglycemic state (glucose level >140 mg per deciliter), overnight time in the target range, the glycated hemoglobin level, and safety events.

RESULTS

A total of 124 participants with a mean (±SD) age of 31.1±5.3 years and a mean baseline glycated hemoglobin level of 7.7±1.2% underwent randomization. The mean percentage of time that the maternal glucose level was in the target range was 68.2±10.5% in the closed-loop group and 55.6±12.5% in the standard-care group (mean adjusted difference, 10.5 percentage points; 95% confidence interval [CI], 7.0 to 14.0; P<0.001). Results for the secondary outcomes were consistent with those of the primary outcome; participants in the closed-loop group spent less time in a hyperglycemic state than those in the standard-care group (difference, −10.2 percentage points; 95% CI, −13.8 to −6.6); had more overnight time in the target range (difference, 12.3 percentage points; 95% CI, 8.3 to 16.2), and had lower glycated hemoglobin levels (difference, −0.31 percentage points; 95% CI, −0.50 to −0.12). Little time was spent in a hypoglycemic state. No unanticipated safety problems associated with the use of closed-loop therapy during pregnancy occurred (6 instances of severe hypoglycemia, vs. 5 in the standard-care group; 1 instance of diabetic ketoacidosis in each group; and 12 device-related adverse events in the closed-loop group, 7 related to closed-loop therapy).

CONCLUSIONS

Hybrid closed-loop therapy significantly improved maternal glycemic control during pregnancy complicated by type 1 diabetes. (Funded by the Efficacy and Mechanism Evaluation Program; AiDAPT ISRCTN Registry number, ISRCTN56898625.)

From the Norfolk and Norwich University Hospitals NHS Foundation Trust (T.T.M.L., H.R.M.) and the Norwich Clinical Trials Unit (C.C., E.F., M.H., L.S.), Norwich Medical School (T.T.M.L., H.R.M.), University of East Anglia, Norwich, Cambridge University Hospitals NHS Foundation Trust (S.H.), and the Wellcome-MRC Institute of Metabolic Science, University of Cambridge (M.E.W., R.H.), Cambridge, the Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds (E.M.S.), the Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow (R.S.L.), King's College Hospital NHS Foundation Trust, London (K.F.H.), the Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast (D.R.M.), Barnard Health Research, Southampton (K.B.-K.), and the Usher Institute (D.R., J.L.) and the Centre for Cardiovascular Science (R.M.R.), University of Edinburgh, Edinburgh — all in the United Kingdom; and the Jaeb Center for Health Research, Tampa, FL (S.B., J.S., C.K., R.B.). Dr. Murphy can be contacted at helen.murphy@uea.ac.uk or at Norwich Medical School, Fl. 2, Bob Champion Research and Education Bldg., Rosalind Franklin Rd., University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, United Kingdom.

*A list of the members of the AiDAPT Collaborative Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 5, 2023, and updated on November 16, 2023, at NEJM.org.

N Engl J Med 2023;389:1566-78.
DOI: 10.1056/NEJMoa2303911

One in two babies born to women with type 1 diabetes have complications, most commonly preterm birth, large birth weight, and admission to the neonatal intensive care unit.[1,2] Maternal antenatal hyperglycemia is the most important risk factor for these complications, with the highest risk seen among persons who begin their pregnancy with above-target glycated hemoglobin levels.[1] Cohort studies and, more recently, intervention trials have unequivocally shown that pregnancy outcomes improve with improved maternal glucose levels.[1-4] However, despite advancements in insulin therapy, continuous glucose monitoring, and high motivation among pregnant persons to manage their diabetes, most pregnant persons with diabetes do not have glucose levels in the pregnancy-specific glucose target range of 63 to 140 mg per deciliter (3.5 to 7.8 mmol per liter), which is lower than the target range of 70 to 180 mg per deciliter (3.9 to 10.0 mmol per liter) for nonpregnant persons.[2,5-7]

Altered eating patterns, marked gestational variations in insulin sensitivity, and stringent pregnancy-specific glucose targets provide formidable challenges for diabetes management during pregnancy.[8-10] Striving for lower glucose levels and the lower pregnancy-specific glucose targets themselves are associated with an increased risk of severe hypoglycemia, a leading cause of maternal morbidity and mortality, whereas hyperglycemia (>140 mg per deciliter) is associated with fetal pancreatic hyperinsulinemia and attendant neonatal complications.[4,11,12]

The use of hybrid closed-loop therapy is associated with improved glucose control in nonpregnant adults and in children,[13] but whether the more stringent glucose targets required for optimal pregnancy outcomes can be achieved with this therapy is unknown. The CamAPS FX is a hybrid closed-loop system that enables automatically adjusted insulin delivery from an insulin pump according to real-time glucose-sensor measurements. This system was approved for use during pregnancy in the United Kingdom on the basis of results from two feasibility studies.[14,15] Subsequently, the system was updated, leading to two key changes: first, glucose measurements from continuous glucose monitors can now be used to inform user-initiated premeal boluses of insulin; second, additional features allow the user to intensify or relax closed-loop insulin delivery and to specify personalized glucose targets, which the user can adjust during pregnancy. We tested whether hybrid closed-loop therapy initiated before 16 weeks' gestation would improve maternal glucose levels during pregnancy complicated by type 1 diabetes.

A Quick Take is available at NEJM.org

Methods

Trial Design

In this open-label, multicenter, randomized, controlled trial, we recruited participants from nine National Health Service sites in England, Scotland, and Northern Ireland. Participants were randomly assigned to receive automated hybrid closed-loop insulin delivery (intervention group) or to continue standard intensive insulin therapy (by means of multiple daily injections or an insulin pump) (standard-care group), with both groups using continuous glucose monitoring.

Approval of the trial protocol, available with the full text of this article at NEJM.org, was received from the Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency. Oversight was provided by an independent trial steering committee. Safety aspects of the trial were reviewed by an independent data monitoring committee. Details of the trial protocol have been published previously.[16]

The Jaeb Center for Health Research was responsible for the randomization scheme, the trial database, data validation, and statistical analyses; the Norwich Clinical Trials Unit was responsible for trial management, data monitoring, and safety outcomes. The trial management committee was responsible for the design of the trial and the decision to submit the manuscript for publication. The first and last authors wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Trial funding was provided by the National Institute for Health and Care Research (NIHR), and continuous glucose monitoring devices were provided by Dexcom at a discounted price. Representatives from Dexcom and the NIHR received a copy of the manuscript before submission but were not permitted to contribute input on the content; no agreements concerning data confidentiality or publication rights were made among the companies, the authors, and their institutions. The statistical analysis plan is included in the protocol. The data included in this manuscript were submitted as academic in confidence to the National

Table 1. Baseline Characteristics of Participants.*

Characteristic	Closed Loop (N=61)	Standard Care (N=63)
Age — yr		
Mean	32.0±5.0	30.2±5.5
Range	19.9–42.7	19.7–44.7
White race — no. (%)†	58 (95)	57 (90)
Duration of diabetes — yr		
Mean	18±8	16±7
Range	2–31	2–33
Body-mass index‡		
Mean	27.9±5.9	26.9±4.8
Range	18.0–48.9	19.9–41.2
Bachelor's degree or equivalent — no. (%)	36 (59)	33 (52)
Week of gestation at recruitment		
Median (IQR)	10.3 (8.0–11.7)	10.0 (8.4–11.3)
Range	6.7–13.7	6.1–14.3
Week of gestation at randomization		
Median (IQR)	11.3 (9.6–13.0)	11.0 (9.6–12.4)
Range	7.7–15.0	7.7–16.3
Medical history		
Diabetes complications — no. (%)	35 (57)	35 (56)
Retinopathy	35 (57)	34 (54)
Nephropathy	4 (7)	5 (8)
Neuropathy	4 (7)	2 (3)
Previous diabetic ketoacidosis — no. (%)§	1 (2)	10 (16)
Previous severe hypoglycemia — no. (%)¶	4 (7)	5 (8)
Chronic hypertension — no. (%)	4 (7)	2 (3)
Systolic blood pressure	117.8±11.9	117.3±12.9
Diastolic blood pressure	69.4±9.3	68.3±9.4
Pregnancy history		
No previous births — no. (%)	21 (34)	38 (60)
Previous pregnancy loss — no. (%)‖	21 (34)	20 (32)
Prepregnancy factors — no. (%)		
Folic acid supplementation	38 (62)	34 (54)
Alcohol consumption	36 (59)	36 (57)
Cigarette smoking	10 (16)	14 (22)
Glycated hemoglobin level during early pregnancy**		
6.0 to <7.0% — no. (%)	23 (38)	13 (21)
7.0 to <8.0% — no. (%)	21 (34)	24 (38)
≥8.0% — no. (%)	17 (28)	26 (41)
Mean	7.6±1.1	7.9±1.3
Range	6.0–11.6	6.5–14.0

Table 1. (Continued.)

Characteristic	Closed Loop (N=61)	Standard Care (N=63)
Continuous glucose monitor — no. (%)	59 (97)	62 (98)
Abbott FreeStyle Libre	43 (73)	47 (76)
Dexcom	12 (20)	14 (23)
Medtronic	4 (7)	1 (2)
Insulin delivery — no. (%)		
Insulin pump	32 (52)	25 (40)
Multiple daily injections	27 (44)	37 (59)
Automated insulin delivery††	2 (3)	1 (2)
Total daily insulin — U/kg/day		
Mean	0.7±0.2	0.7±0.2
Range	0.3–1.3	0.3–1.4

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Race was reported by the participant.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The previous diabetic ketoacidosis events were counted if they occurred in the 12 months before enrollment.
¶ Hypoglycemia was considered severe if the event required third-party assistance; severe hypoglycemia events were counted if they occurred in the 12 months before enrollment.
‖ This category includes previous miscarriages and pregnancy terminations.
** One participant with a glycated hemoglobin level of 6.0% was enrolled during the Covid-19 pandemic (in March 2020); at the time, this patient had frequent hypoglycemic events while using an alternative closed-loop (Tandem Control-IQ) system.
†† Participants using alternative hybrid closed-loop systems were eligible.

Institute for Health and Clinical Excellence Diagnostics Assessment team, for the assessment of hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes.

TRIAL PARTICIPANTS

We recruited pregnant women, 18 to 45 years of age, who had had type 1 diabetes for at least 12 months; women were recruited as soon as possible after confirmation by ultrasonography of a viable pregnancy and before 14 weeks' gestation. Participants who were receiving intensive insulin therapy administered by means of either multiple daily injections or an insulin pump were eligible to enroll in the trial if they had a glycated hemoglobin level of at least 6.5% during early pregnancy and a level of 10% or less at randomization. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Screening and Run-In Period

Participants were screened for eligibility by local clinic teams. The glycated hemoglobin level was measured at each site with the use of a method that was recommended by the International Federation of Clinical Chemistry and Laboratory Medicine. All participants provided written informed consent.

After recruitment, participants completed a 4-to-10-day run-in period to provide a baseline glycemic assessment (≥96 hours of glucose values, including 24 hours overnight) and to ensure that continuous glucose monitoring was not associated with unacceptable effects. Baseline glucose values were masked for both participants and investigators, except for values in participants who were using fingerstick or another method of glucose monitoring as part of routine clinical care and in those who were already using the same continuous glucose monitor that was being used in the trial. Diabetes and obstetrical history, results of a brief physical examination, and patient-reported outcomes were recorded.

Randomization

Eligible participants underwent randomization 1 to 2 weeks after recruitment and before 16 weeks' gestation. Treatments were assigned in a

Table 2. Primary and Secondary Maternal Glucose Outcomes.*

Outcomes	Baseline†		Antenatal Intervention Phase‡		
	Closed Loop (N=59)	Standard Care (N=59)	Closed Loop (N=59)	Standard Care (N=61)	Adjusted Treatment Difference (95% CI)§
Primary outcome					
Percentage of time with glucose level in range 63–140 mg/dl	47.8±16.4	44.5±14.4	68.2±10.5	55.6±12.5	10.5 (7.0 to 14.0)¶
Key secondary outcomes					
Percentage of time with glucose level >140 mg/dl	48.7±18.0	51.8±16.2	29.2±10.6	41.4±13.2	−10.2 (−13.8 to −6.6)
Percentage of overnight time with glucose level in range 63–140 mg/dl (11 p.m. to 7 a.m.)†	47.4±20.8	44.5±16.6	70.8±11.2	56.7±13.6	12.3 (8.3 to 16.2)
Other secondary outcomes					
Percentage of time with glucose level in range 63–180 mg/dl	71±16	68±15	87±9	80±10	6 (3 to 9)
Percentage of time with glucose level >180 mg/dl	26±17	28±16	11±9	17±11	−5 (−8 to −3)
Glucose area under the curve >120 mg/dl	39.5±23.7	41.3±19.7	19.3±12.2	27.9±12.9	−7.4 (−11.1 to −3.7)
Mean glucose level — mg/dl‖	149±28	151±24	125±14	136±16	−9.2 (−13.7 to −4.7)
Glycated hemoglobin level — %	7.6±1.1	7.9±1.3	6.0±0.5	6.4±0.5	−0.3 (−0.5 to −0.1)
Glucose SD — mg/dl**	54±14	55±12	42±11	47±10	−4.5 (−7.3 to −1.6)
Glucose coefficient of variation — %	36±5	37±6	33±5	34±5	−1.1 (−2.5 to 0.3)
Hypoglycemia					
Median percentage of time with glucose level <63 mg/dl (IQR)	2.75 (0.86 to 4.87)	2.22 (0.72 to 6.00)	2.26 (1.54 to 3.31)	2.02 (1.25 to 4.37)	−0.43 (−1.04 to 0.19)
Median percentage of time with glucose level <54 mg/dl (IQR)	1.05 (0.07 to 2.37)	0.79 (0.18 to 2.28)	0.71 (0.49 to 1.19)	0.73 (0.36 to 1.67)	−0.23 (−0.55 to 0.09)
Median no. of mild hypoglycemia events (IQR)††	6.4 (2.2 to 11.5)	5.5 (2.4 to 11.1)	6.7 (4.6 to 9.4)	5.7 (3.1 to 9.4)	0.1 (−1.1 to 1.3)
Median no. of moderate hypoglycemia events (IQR)††	2.2 (0.0 to 5.7)	2.2 (0.0 to 5.9)	2.3 (1.6 to 3.8)	2.1 (1.1 to 4.4)	0.0 (−0.7 to 0.7)

Overnight outcomes (11 p.m. to 7 a.m.)					
Mean glucose level — mg/dl	149±33	150±26	125±14	135±17	−8.9 (−13.6 to −4.2)
Percentage of time with glucose level >140 mg/dl	49±22	52±18	27±11	40±14	−11 (−15 to −7)
Median percentage of time with glucose level <63 mg/dl (IQR)	1.40 (0.00 to 5.27)	2.33 (0.51 to 5.67)	1.56 (1.10 to 2.51)	2.57 (1.04 to 4.41)	−1.37 (−2.13 to −0.60)
Glucose SD — mg/dl	52±17	54±14	40±12	47±12	−5.8 (−9.3 to −2.3)
Glucose coefficient of variation — %	35±8	36±8	32±5	35±6	−2.4 (−4.2 to −0.5)
Median no. of hypoglycemia events (IQR)††					
Mild	3.5 (0.0 to 10.2)	6.4 (0.0 to 11.9)	4.3 (2.9 to 5.5)	5.3 (2.8 to 8.7)	−1.7 (−3.0 to −0.5)
Moderate	0.0 (0.0 to 4.7)	0.0 (0.0 to 6.9)	1.7 (1.0 to 2.5)	2.1 (0.8 to 4.3)	−0.7 (−1.4 to −0.0)

* Plus–minus values are means ±SD. The median number of hours of sensor data available in the closed-loop group was 150 hours (IQR, 128 to 156) at baseline and 3361 (IQR, 2996 to 3561) during the antenatal intervention phase, and in the standard-care group the median was 149 hours (IQR, 124 to 171) at baseline and 3417 (IQR, 3112 to 3507) during the antenatal intervention phase.

† Baseline values were calculated with the use of data assessed by continuous glucose monitoring during the prerandomization run-in phase. Two participants were missing baseline data assessed by continuous glucose monitoring. Four participants whose follow-up data assessed by continuous glucose monitoring were missing because of a miscarriage, pregnancy termination, or both are not included here.

‡ The antenatal intervention phase is from 16 weeks' gestation until delivery. Outcomes were calculated with the use of sensor data assessed by continuous glucose monitoring except for the glycated hemoglobin level, which was measured at the trial sites. Four participants were missing intervention data assessed by continuous glucose monitoring. The glycated hemoglobin level at 34 to 36 weeks' gestation reflects maternal levels over the preceding 10 to 12 weeks.

§ The model was adjusted for baseline value, insulin delivery method, and site as a random effect. Differences in outcomes that were measured as percentages are given in percentage points. P<0.001 for the between-group comparison of the primary outcome.

¶ Results were similar when adjustment was made for the number of previous diabetic ketoacidosis events, when previous pregnancies were considered as covariates, and when site was treated as a fixed effect (mean difference, 10.6 percentage points; 95% CI, 7.0 to 14.1).

‖ Shown are the means of the individual participants' mean glucose levels.

** The glucose SD and coefficient of variation values indicate within-participant variability of continuous glucose monitor measurements.

†† Mild hypoglycemia was defined as a glucose level of less than 63 mg per deciliter (3.5 mmol per liter) as assessed by continuous glucose monitoring for at least 15 consecutive minutes, with episodes separated by 30 minutes or more. Moderate hypoglycemia was defined as a glucose level of less than 54 mg per deciliter (3.0 mmol per liter) as assessed by continuous glucose monitoring for at least 15 consecutive minutes, with episodes separated by 30 minutes or more.

1:1 ratio by means of a Web-based system that used a computer-generated randomization list with permuted block sizes of 2 and 4 and with stratification by clinical site.

TREATMENTS

Closed-Loop System Group

The hybrid closed-loop system comprised a smartphone (Galaxy S8 through S12, Samsung) provided to participants or, if participants preferred, their own smartphone, hosting the CamAPS FX application (CamDiab), which ran the Cambridge model predictive control algorithm (version 0.3.71). The smartphone communicated by means of Bluetooth with both the Dana Diabecare RS insulin pump (Sooil) and the Dexcom G6 continuous glucose monitor (Dexcom). Participants were trained in the use of the closed-loop system by the research educator or by local teams. Personal glucose targets were specified by the participants; we recommended a target of 100 mg per deciliter (5.5 mmol per liter) in early pregnancy, reducing the target to 81 to 90 mg per deciliter (4.5 to 5.0 mmol per liter) between 16 and 20 weeks' gestation, and continuing with the use of the lower targets until delivery.

Standard-Care Group

Participants in the standard-care group continued multiple daily injections or insulin-pump therapy with insulin dose adjustment as directed by their local teams, which aimed for standard glucose targets (63 to 100 mg per deciliter before meals and <140 mg per deciliter 1 hour after meals). Local teams provided training on the use of continuous glucose monitoring and insulin-dose adjustment. The technical support and training resources that were provided to the trial staff and participants are outlined in the Supplementary Appendix.

The trial flowchart and visit schedules are provided in Figure S1 in the Supplementary Appendix. Virtual training and visit options were added during the coronavirus disease 2019 (Covid-19) pandemic. After randomization, participants had in-person or virtual (telephone or video call) trial visits every 4 weeks. Additional visits or contacts occurred as clinically indicated. Glycated hemoglobin measurements were repeated locally at 24 and 36 weeks, and follow-up questionnaires were obtained at 34 to 36 weeks' gestation.

OUTCOMES

The primary efficacy outcome was the percentage of time in the pregnancy-specific target glucose range of 63 to 140 mg per deciliter from 16 weeks' gestation until delivery. Key secondary outcomes were the percentage of time spent in a hyperglycemic state (glucose level >140 mg per deciliter) and the percentage of overnight time in the target glucose range. A prespecified subset of outcomes as measured by glucose sensors (mean glucose level; the percentage of time spent in, above, and below relevant thresholds; glycemic variability; and hypoglycemic events) were calculated for overnight time (11 p.m. to 7 a.m.) and for each trimester. Additional secondary outcomes included glycated hemoglobin levels, insulin doses, and glucose-sensor targets. Secondary outcomes are listed in the statistical analysis plan and the Supplementary Appendix.

Safety outcomes included severe hypoglycemia, diabetic ketoacidosis, and device-related adverse events. Maternal and neonatal outcomes were documented after delivery, at hospital discharge.

STATISTICAL ANALYSIS

We calculated that with 98 enrolled participants, the trial would have 90% power to detect an absolute difference of 10 percentage points in the primary outcome (percentage of time in the pregnancy-specific target glucose range) from 16 weeks' gestation until delivery, with a standard deviation of 15% and a two-sided type I error rate of 5%. We increased this sample size to 124 to allow for pregnancy loss and for withdrawal from the trial for other reasons.

Statistical analyses were performed on an intention-to-treat basis and included all participants with at least 96 hours of glucose-sensor data between 16 weeks' gestation and delivery. For each outcome, the groups were compared with the use of a linear mixed-effects regression model, with the percentage of time in the target range at baseline, insulin delivery, and clinical site as a random effect. Missing data were handled with the use of multiple imputation and a pattern-mixture model; all participants who underwent randomization were included in the group to which they were randomly assigned, regardless of treatment adherence. A per-protocol analysis was performed with the use of an inverse probability of treatment weighting ap-

proach including participants who met the analysis requirements described in the protocol.[17] All P values were two-sided. Confidence intervals for the secondary outcomes were not adjusted for multiplicity and should not be used to infer definitive treatment effects. Analyses were performed with the use of SAS, version 9.4.

RESULTS

PARTICIPANTS

From September 2019 through May 2022, a total of 334 participants were assessed for eligibility. Among 199 potentially eligible participants, 126 were enrolled and 124 underwent randomization, with 61 assigned to the closed-loop group and 63 to the standard-care group (Fig. S2). Participants were from nine maternity clinics, were a mean (±SD) 31.1±5.3 years of age, and had a mean baseline glycated hemoglobin level of 7.7±1.2%. They were representative of pregnant persons with type 1 diabetes in the United Kingdom (Table 1 and Tables S1 through S3). Almost all the participants (98%) were using continuous glucose monitoring, and approximately half were using insulin-pump therapy at enrollment. Participants in the closed-loop group had more previous pregnancies, whereas those in the standard-care group reported more previous diabetic ketoacidosis events.

Two participants did not adhere to their assigned treatment; Covid-19 lockdown restrictions prevented one participant in the closed-loop group from receiving closed-loop training, and one participant in the standard-care group procured automated insulin delivery (CamAPS FX) outside the trial. Seven participants in each group discontinued their assigned treatment (the timing and reasons are listed in Table S4).

Despite the effect of the Covid-19 pandemic, the percentage of completed trial visits was approximately 95% from 16 weeks' gestation until delivery (Fig. S3). Participants in the standard-care group had more additional clinic visits than those in the closed-loop group (1.5 vs. 1.1) and more unscheduled contacts (9.6 vs. 6.1), mostly for pregnancy and diabetes-related reasons (Tables S5 and S6). The median percentage of time participants used continuous glucose monitoring was 97% across both treatment groups (Table S7 and Fig. S4). The median percentage of time participants used the closed-loop system was 96% and remained higher than 95% throughout pregnancy (Table S8 and Fig. S5).

PRIMARY OUTCOME

The mean (±SD) percentage of time that maternal glucose levels were within the pregnancy-specific target range differed between trial groups, increasing from 47.8±16.4% at baseline to 68.2±10.5% during the treatment period in the closed-loop group and from 44.5±14.4% at baseline to 55.6±12.5% during the treatment period in the standard-care group (mean adjusted difference between the groups over the course of the treatment period, 10.5 percentage points; 95% CI, 7.0 to 14.0; P<0.001) (Table 2 and Fig. S6).

No variations were seen in the treatment effect among trial sites, and no differential effects across maternal age, glycated hemoglobin, or insulin delivery categories were seen (Fig. S7). The treatment difference was consistent between the intention-to-treat and per-protocol analyses (Table S9). A post hoc analysis with site as a fixed effect produced similar results (Table S17).

SECONDARY GLYCEMIC OUTCOMES

Participants randomly assigned to the closed-loop group spent less time with glucose levels above the target range than those assigned to the standard-care group (mean difference, −10.2 percentage points; 95% CI, −13.8 to −6.6) (Table 2). The effects of the intervention on the percentage of time spent in the target range during the overnight period (11 p.m. to 7 a.m.) were similar to the 24-hour results (mean difference, 12.3 percentage points; 95% CI, 8.3 to 16.2). These effects were accompanied by improved control among participants in the closed-loop group, including a lower mean glucose level, lower glycated hemoglobin level, and fewer nocturnal hypoglycemic events than were seen in the standard-care group (Table S10); these results are notable because participants spent approximately 70% of the time in the target range (63 to 180 mg per deciliter) at baseline. Furthermore, participants who started closed-loop therapy during the first trimester spent 5% more time in the target range by the end of 12 weeks' gestation than those in the standard-care group (Fig. 1 and Table S11).

A total of 28 participants (47%) in the closed-loop group and 7 (11%) in the standard-care group spent more than 70% of each day (16

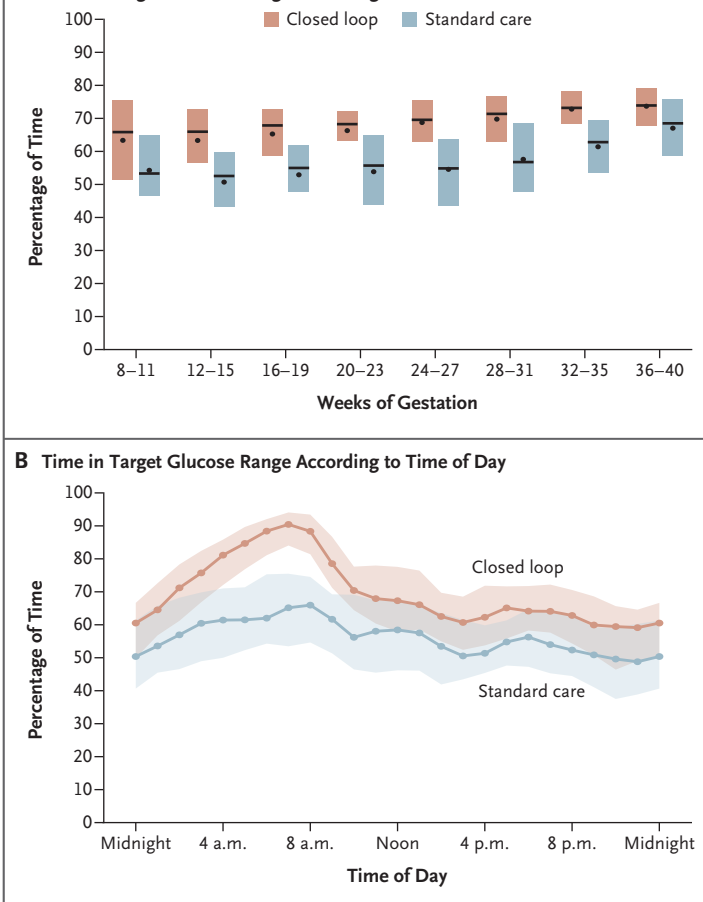

Figure 1. Percentage of Time in the Pregnancy-Specific Target Glucose Range.

Panel A shows box plots of the percentage of time that the glucose level was within the pregnancy-specific target glucose range of 63 to 140 mg per deciliter (3.5 to 7.8 mmol per liter), as measured by continuous glucose monitoring, for each treatment group, over each 4-week antenatal period from the time the participant was trained in the use of the device until delivery. The mean personal glucose targets used by participants in the closed-loop group during their first, second, and third trimesters were 102 mg per deciliter, 97 mg per deciliter, and 93 mg per deciliter (5.7 mmol per liter, 5.4 mmol per liter, and 5.1 mmol per liter, respectively). Black bars indicate medians, black dots means, and the top and bottom of the boxes the interquartile range. Panel B shows an envelope plot of the same outcome (time in the pregnancy-specific target glucose range), as measured by continuous glucose monitoring, for each treatment group, according to the time of day, from 16 weeks' gestation until delivery. Shaded areas indicate the interquartile range.

hypoglycemia, weight gain, or total daily insulin dose (Tables 2 and 3 and Tables S13 and S14). There were no between-group differences in patient-reported outcomes (Table S15).

MATERNAL AND NEONATAL OUTCOMES

One instance of shoulder dystocia occurred in a baby born to a participant in the closed-loop group. One neonatal death, from hypoxic ischemic encephalopathy, and three serious birth injuries (three other hypoxic ischemic encephalopathy events) occurred among babies born to participants in the standard-care group (Table 3). We observed fewer cases of new-onset hypertension and more repeat cesarean sections (scheduled before the onset of labor) among participants in the closed-loop group than among those in the standard-care group, most likely related to the participants' previous pregnancies. Babies delivered by participants in the closed-loop group were born an average of 4.5 days earlier than those delivered by participants in the standard-care group, with no differences observed in the number of preterm births, in birth weight, in neonatal complications, or in admissions to the neonatal intensive care unit.

SAFETY OUTCOMES

Six severe hypoglycemia events occurred in the closed-loop group and five in the standard-care group (Table 4). One diabetic ketoacidosis event occurred in each group. One participant with severe hyperemesis had 20 nonacidotic ketosis events. She did not use the closed-loop system between 16 weeks' gestation and delivery but contributed to the greater number of ketosis and serious adverse events in the closed-loop group than in the standard-care group. The rate of device-related adverse events in the closed-loop system was 24.3 per 100 person-years; 12 device-related events occurred in the closed-loop group — 2 related to both the closed-loop system and the continuous glucose monitor, 5 related to only the closed-loop system, and 5 related to only the continuous glucose monitor (Table S16).

DISCUSSION

We found that the percentage of time that glucose levels were within the pregnancy-specific target range of 63 to 140 mg per deciliter from 16 weeks' gestation until delivery was 10.5 percentage points higher (an additional 2.5 hours hours 48 minutes) within the pregnancy-specific target glucose range (Table S12). Improvements in maternal glycemic control were achieved with participants lowering their mean personal glucose targets (from 102±2 to 93±5 mg per deciliter) throughout pregnancy and without additional

Table 3. Maternal and Neonatal Outcomes.*

Outcome	Closed Loop (N=59)	Standard Care (N=60)
Maternal outcomes		
Any hypertensive disorder — no. (%)	12 (20)	25 (42)
Worsening of existing hypertension	4 (7)	2 (3)
New onset hypertension	6 (10)	19 (32)
Preeclampsia	4 (7)	12 (20)
Mode of delivery — no. (%)†		
Vaginal	10 (17)	15 (25)
Primary cesarean section	24 (41)	34 (57)
Repeat cesarean section	25 (42)	11 (18)
Cesarean type — no./total no. (%)		
Planned or elective	27/49 (55)	22/45 (49)
Unplanned or emergency	22/49 (45)	23/45 (51)
Maternal weight gain — kg	11.1±6.1	14.1±6.1
Median length of hospital stay (IQR) — days	6 (4–9)	6 (4–8)
Fetal and neonatal outcomes		
Pregnancy loss at <20 wk — no.‡	1	3
Neonatal death — no.§	0	1
Baby alive at discharge — no./total no. (%)¶	59/60 (98)	59/63 (94)
Gestational age at delivery	36 wk 3 days (±2 wk)	37 wk 1 day (±1 wk)
Preterm birth, at <37 wk — no./total no. (%)‖	27/60 (45)	14/63 (22)
Birth weight**		
Mean — kg	3.3±0.6	3.5±0.5
Median customized percentile (IQR)	80.7 (53–97)	90.1 (71–99)
Small for gestational age — no. (%)	3 (5)	1 (2)
Large for gestational age — no. (%)	23 (39)	30 (50)
Extremely large for gestational age — no. (%)	13 (22)	19 (32)
Macrosomia >4.0 kg — no. (%)	4 (7)	9 (15)
Neonatal complications		
Serious birth injury — no. (%)††	1 (2)	4 (7)
Respiratory distress — no. (%)	5 (8)	8 (13)
Hypoglycemia treated with intravenous or oral glucose — no. (%)	26 (44)	25 (42)
Hyperbilirubinemia — no. (%)	40 (68)	37 (62)
Readmission within 7 days — no. (%)	8 (14)	3 (5)
Neonatal intensive care unit stay ≥1 day — no. (%)	13 (22)	15 (25)
Median length of hospital stay (IQR) — days	6 (3–10)	5 (3–7)

* Plus–minus values are means ±SD.
† Mothers in the closed-loop group had more previous births, which most likely contributed to more repeat (scheduled before the onset of labor) cesarean deliveries.
‡ One first trimester miscarriage occurred in each group and two pregnancies were terminated in the standard-care group.
§ Neonatal death occurred approximately 12 hours after birth, after the onset of early preterm labor and severe hypoxic ischemic encephalopathy at 31 weeks' gestation.
¶ The percentages for "baby alive at discharge" are based on the numbers for all fetuses and neonates, whether they were born alive or not.
‖ The percentages for "preterm birth" do not include pregnancy losses before 20 weeks' gestation.
** Birth weight was calculated with the use of gestation-related optimal weight (version 8.0.6.2) percentiles that adjust for neonatal sex, gestation duration, maternal height, weight, parity, and ethnicity. Small for gestational age is defined as weight less than the 10th percentile, large for gestational age as weight higher than the 90th percentile, and extremely large for gestational age as weight higher than the 97.7th percentile.
†† The birth injuries were one shoulder dystocia (additional maneuvers required to release the shoulders) in the closed-loop group and four hypoxic ischemic encephalopathy events (including one death) in the standard-care group.

Table 4. Safety Outcomes.

Outcome	Closed Loop	Standard Care
Severe hypoglycemia		
No. of events	6	5
Participants with ≥1 event	4	5
Incidence per 100 person-yr	20.8	16.4
Hyperglycemia or ketosis		
No. of events	34	8
Mild to moderate*	8	5
Severe†	25	2
Diabetic ketoacidosis‡	1	1
Participants with ≥1 event	11	6
Participants with 1 event	7	5
Participants with ≥2 events	4	1
Incidence of diabetic ketoacidosis per 100 person-yr	3.5	3.3
Serious adverse events§		
Total no. of events	34	14
Hyperglycemia or ketosis	22	3
Hypoglycemia	3	1
Other	9	10
Participants with ≥1 event	10	9
Incidence per 100 person-yr	118.1	45.9
Device-related adverse events with the closed-loop system		
No. of events¶	7	NA
Participants with ≥1 event	7	NA
Incidence per 100 person-yr	24.3	NA
Device-related adverse events with the continuous glucose monitor		
No. of events	7	9
Participants with ≥1 event	7	7
Incidence per 100 person-yr	24.3	29.5

* Mild-to-moderate events include ketosis (ketones >0.5 mmol per liter) that were treated by the participant and resolved without hospital admission.

† Severe ketosis was defined as a level of plasma ketones above 1.0 mmol per liter that resulted in hospital admission and treatment with intravenous insulin. One participant had 20 events, none of which occurred while using closed-loop therapy.

‡ Diabetic ketoacidosis was defined as ketosis with acidosis that resulted in treatment with fixed-rate intravenous insulin infusion.

§ Serious adverse events were defined as adverse events that resulted in death, a serious deterioration in health, life-threatening illness or injury, permanent impairment, in-patient or prolonged hospitalization, fetal distress, fetal death, or fetal congenital anomaly. One participant had 19 ketosis serious adverse events, none of which occurred while she was using closed-loop therapy.

¶ Twelve device-related adverse events occurred in the closed-loop group — 2 related to both the closed-loop system and the continuous glucose monitor, 5 related to only the closed-loop system, and 5 related to only the continuous glucose monitor. The device-related adverse events in the closed-loop group included an incorrect insulin bolus that a participant administered to herself, resulting in severe hypoglycemia after a miscarriage; one hyperglycemic event that contributed to a participant stopping closed-loop treatment on the 17th day after randomization; and one moderate ketosis event after the overnight loss of Bluetooth connectivity the day before admission for a preterm birth. Other events relating to sensor failures, infusion set failures, or both were not serious (see Table S16 in the Supplementary Appendix).

per day) among participants assigned to closed-loop therapy than among those assigned to continuous glucose monitoring alongside their usual insulin-delivery method. The time-in-range benefits were achieved by a reduction in maternal hyperglycemia and an increase in nocturnal time in the target range. Improvements in glucose outcomes were consistent across baseline maternal age, glycated hemoglobin levels, clinical sites, and pretrial insulin-delivery method. Furthermore, there was no increase in gestational weight gain or maternal insulin doses with closed-loop therapy. The incidence of hypoglycemia was low at baseline, and apart from a lower incidence of nighttime hypoglycemia events in the closed-loop group than in the standard-care group, did not differ between groups. Among patients receiving closed-loop therapy, an increase of 5 percentage points in the time in the target range was apparent by the end of the first trimester, which suggests that the benefits occurred soon after initiation of closed-loop therapy (which occurred at approximately 12 weeks' gestation); this time frame is crucially important for women and clinicians considering therapeutic changes during early pregnancy.

The trial was conducted during the Covid-19 pandemic, which particularly affected pregnant persons, and necessitated rapid implementation of virtual training and visits. Nonetheless, use of the closed-loop system was high (>95%) throughout pregnancy and without apparent safety problems, including among participants who were new to insulin-pump therapy. Participants who continued standard care had more clinic visits and more unscheduled contacts, which suggests that beyond initial training, use of the closed-loop system did not require additional input from health care professionals.[18,19]

Recent trials have shown the benefits of closed-loop therapy in persons with newly diagnosed type 1 diabetes and young children, and these results extend the evidence to pregnant women.[20,21] Alongside the participants' motivation to minimize pregnancy complications, closed-loop therapy facilitated attainment of glucose levels in the pregnancy-specific target range 70% of the time. Given the rapid increase in the time in the target range observed within 1 week after initiation of therapy in this trial, and within 1 day in a recent trial,[22] we speculate that further benefits may be obtained from starting closed-loop therapy before pregnancy or as soon as possible after pregnancy is confirmed. Participants were offered the option to continue closed-loop therapy during the inpatient admission for labor and delivery (results not reported here).

The participants in the current trial gained an additional 10 percentage points of time in the target range above the 10 percentage-point increment seen with continuous glucose monitoring and standard insulin therapy during pregnancy. Previous studies have shown that every increase of 5 percentage points of the time in the target range is associated with improved obstetrical and neonatal outcomes.[23] Our trial was not powered for pregnancy outcomes, but we infer that this additional 10 percentage points of time in the pregnancy-specific target range would be expected to have additional health benefits for pregnant persons and their babies.

Strengths of our trial include its randomized, controlled design; the generalizability of our population, which included participants who had not previously received insulin-pump therapy; a large percentage of participants who initiated therapy during the first trimester; and a flexible trial protocol that facilitated virtual or in-person visits. We observed no increase in clinical contacts, which is often observed in trials of investigational devices.

This trial had certain limitations. The sample size did not provide definitive data on maternal and neonatal health outcomes. Most of the participants (93%) were White, participants were excluded if they did not have a glycated hemoglobin level of 10% or less by the time of randomization, and 56% of the participants had an undergraduate or equivalent education. First-trimester data were limited because participants underwent randomization at a median of 11 weeks' gestation. We did not record the use of the CamAPS Boost and Ease-Off features of the closed-loop system, and data cannot be extrapolated to systems with higher glucose-level targets.

In this trial, closed-loop therapy was effective during pregnancy complicated by type 1 diabetes, accounting for the marked gestational changes in insulin doses in trial participants, and provided a clinical advantage beyond that achieved with continuous glucose monitoring and insulin-pump therapy. These results support the recommendations, proposed in the guideline from

the National Institute for Health Care Excellence, that hybrid closed-loop therapy should be offered to all pregnant persons with type 1 diabetes.

The views expressed in this publication are those of the authors and not necessarily those of the Medical Research Council (MRC), National Institute for Health and Care Research (NIHR), or the Department of Health and Social Care.

Supported by the Efficacy and Mechanism Evaluation (EME) Program, an MRC and NIHR partnership (NIHR EME reference 16/35/01). The trial data management and statistical center were supported from JDRF awards #22-2013-266 and #2-RSC-2019-828-M-N. Dr. Lee is funded by a Diabetes Research & Wellness Foundation Sutherland-Earl Clinical Fellowship (SECF/21).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the trial participants and their partners who have supported our research; our Patient Public Involvement contributors, Sarah Cains and Goher Ayman, for their input through the trial steering committee throughout the trial, and Jessica Rusnak; Mercedes Mills (Research and Innovation services, University of East Anglia, Norwich, United Kingdom) for assistance with the complex legal, financial, and contractual issues; and Professor Jason Gardosi and his colleagues at the United Kingdom Perinatal Institute for granting access to the latest version of the gestation-related optimal weight customized birth-weight percentiles. This article is dedicated to our friend and collaborator Professor Fiona Denison (University of Edinburgh, Scotland), who died during the trial, after Covid-19 devastated her mental health and well-being.

REFERENCES

1. Murphy HR, Howgate C, O'Keefe J, et al. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. Lancet Diabetes Endocrinol 2021;9:153-64.

2. Mathiesen ER, Alibegovic AC, Corcoy R, et al. Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial. Lancet Diabetes Endocrinol 2023;11:86-95.

3. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347-59.

4. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004;328:915.

5. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593-603.

6. Tundidor D, Meek CL, Yamamoto J, et al. Continuous glucose monitoring time-in-range and HbA_{1c} targets in pregnant women with type 1 diabetes. Diabetes Technol Ther 2021;23:710-4.

7. O'Malley G, Ozaslan B, Levy CJ, et al. Longitudinal observation of insulin use and glucose sensor metrics in pregnant women with type 1 diabetes using continuous glucose monitors and insulin pumps: the LOIS-P study. Diabetes Technol Ther 2021;23:807-17.

8. Scott EM, Murphy HR, Kristensen KH, et al. Continuous glucose monitoring metrics and birth weight: informing management of type 1 diabetes throughout pregnancy. Diabetes Care 2022;45:1724-34.

9. Murphy HR, Elleri D, Allen JM, et al. Pathophysiology of postprandial hyperglycaemia in women with type 1 diabetes during pregnancy. Diabetologia 2012;55:282-93.

10. Goudie RJ, Lunn D, Hovorka R, Murphy HR. Pharmacokinetics of insulin aspart in pregnant women with type 1 diabetes: every day is different. Diabetes Care 2014;37(6):e121-e122.

11. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GH. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. Diabetes Care 2002;25:554-9.

12. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, Damm P, Mathiesen ER. Hypoglycaemia during pregnancy in women with Type 1 diabetes. Diabet Med 2012;29:558-66.

13. Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. Endocr Rev 2023;44:254-80.

14. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. N Engl J Med 2016;375:644-54.

15. Stewart ZA, Wilinska ME, Hartnell S, et al. 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 2018;41:1391-9.

16. Lee TTM, Collett C, Man M-S, et al. AiDAPT: automated insulin delivery amongst pregnant women with type 1 diabetes: a multicentre randomized controlled trial — study protocol. BMC Pregnancy Childbirth 2022;22:282.

17. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.

18. Lawton J, Rankin D, Hartnell S, et al. Healthcare professionals' views about how pregnant women can benefit from using a closed-loop system: qualitative study. Diabet Med 2023;40(5):e15072.

19. Rankin D, Hart RI, Kimbell B, et al. Rollout of closed-loop technology to pregnant women with type 1 diabetes: healthcare professionals' views about potential challenges and solutions. Diabetes Technol Ther 2023;25:260-9.

20. Ware J, Allen JM, Boughton CK, et al. Randomized trial of closed-loop control in very young children with type 1 diabetes. N Engl J Med 2022;386:209-19.

21. Boughton CK, Allen JM, Ware J, et al. Closed-loop therapy and preservation of c-peptide secretion in type 1 diabetes. N Engl J Med 2022;387:882-93.

22. Wadwa RP, Reed ZW, Buckingham BA, et al. Trial of hybrid closed-loop control in young children with type 1 diabetes. N Engl J Med 2023;388:991-1001.

23. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. Diabetologia 2019;62:1123-8.