

Closed-Loop Insulin Delivery During Pregnancy Complicated by Type 1 Diabetes

HELEN R. MURPHY, MD¹
 DANIELA ELLERI, MD^{1,2}
 JANET M. ALLEN, RN¹
 JULIE HARRIS, RN¹
 DAVID SIMMONS, MD³
 GERRY RAYMAN, MD⁴

ROSEMARY TEMPLE, FRCP⁵
 DAVID B. DUNGER, MD²
 AHMAD HAIDAR, MSCA¹
 MARIANNA NODALE, MSC¹
 MALGORZATA E. WILINSKA, PHD^{1,2}
 ROMAN HOVORKA, PHD^{1,2}

OBJECTIVE—This study evaluated closed-loop insulin delivery with a model predictive control (MPC) algorithm during early (12–16 weeks) and late gestation (28–32 weeks) in pregnant women with type 1 diabetes.

RESEARCH DESIGN AND METHODS—Ten women with type 1 diabetes (age 31 years, diabetes duration 19 years, BMI 24.1 kg/m², booking A1C 6.9%) were studied over 24 h during early (14.8 weeks) and late pregnancy (28.0 weeks). A nurse adjusted the basal insulin infusion rate from continuous glucose measurements (CGM), fed into the MPC algorithm every 15 min. Mean glucose and time spent in target (63–140 mg/dL), hyperglycemic (>140 to ≥180 mg/dL), and hypoglycemic (<63 to ≤50 mg/dL) were calculated using plasma and sensor glucose measurements. Linear mixed-effects models were used to compare glucose control during early and late gestation.

RESULTS—During closed-loop insulin delivery, median (interquartile range) plasma glucose levels were 117 (100.8–154.8) mg/dL in early and 126 (109.8–140.4) mg/dL in late gestation ($P = 0.72$). The overnight mean (interquartile range) plasma glucose time in target was 84% (50–100%) in early and 100% (94–100%) in late pregnancy ($P = 0.09$). Overnight mean (interquartile range) time spent hyperglycemic (>140 mg/dL) was 7% (0–40%) in early and 0% (0–6%) in late pregnancy ($P = 0.25$) and hypoglycemic (<63 mg/dL) was 0% (0–3%) and 0% (0–0%), respectively ($P = 0.18$). Postprandial glucose control, glucose variability, insulin infusion rates, and CGM sensor accuracy were no different in early or late pregnancy.

CONCLUSIONS—MPC algorithm performance was maintained throughout pregnancy, suggesting that overnight closed-loop insulin delivery could be used safely during pregnancy. More work is needed to achieve optimal postprandial glucose control.

Diabetes Care 34:406–411, 2011

For women with type 1 diabetes, self-management is particularly challenging during the physiologic and hormonal changes of pregnancy. These contribute to extremely labile glucose levels in early pregnancy and progressive insulin resistance with advancing gestation (1). Continuous glucose monitoring

(CGM) studies indicate that pregnant women with type 1 diabetes spend an average of 10 h daily with glucose levels outside the recommended target (63–140 mg/dL) even with apparently safe A1C levels (2). Hence, their pregnancy outcomes remain suboptimal, with increased risks both of adverse pregnancy outcome

(congenital malformation, stillbirth, neonatal death) and of perinatal morbidity (preterm delivery, macrosomia, neonatal care admission) (3,4).

Strict glycemic control targets are more readily achievable by pregnant women with type 2 diabetes, with recent studies demonstrating improvements both in adverse pregnancy outcome and in perinatal morbidity (5). In contrast, there has been a disappointing lack of progress in type 1 diabetes, most likely due to a more severe glycemic disturbance (6). Hence, despite educational (structured education and prepregnancy care programs) and technologic advances (fast-acting insulin analogs, insulin pump therapy), suboptimal glycemic control and poor pregnancy outcomes persist (7–9).

Insulin pump therapy, CGM, and sensor-augmented pump therapy have been shown to facilitate improved glycemic control in nonpregnant individuals (10–12). However, despite evidence supporting CGM in pregnancy, the benefits of insulin pump therapy are not well established, particularly during late pregnancy (13–15). This may be due to difficulties responding to the physiologic challenges of pregnancy, such as changes in gastric emptying, gluconeogenesis, and insulin kinetics (16).

Closed-loop systems use a control algorithm to link insulin delivery with real-time CGM measurements (17). Overnight use improved glucose control and reduced hypoglycemia in children with type 1 diabetes (18). A closed-loop system with physiologically responsive insulin adjustments capable of maintaining near-normal glucose levels could be of great benefit for pregnant women with type 1 diabetes.

Obstacles to developing closed-loop systems in pregnancy include a lack of sensor accuracy data and no data regarding performance of control approaches such as the model predictive control (MPC) algorithm. Previous studies documented clinically acceptable accuracy of real-time CGM outside of pregnancy but have compared only retrospective CGM

From the ¹Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Hills Road, Cambridge, U.K.; the ²Department of Paediatrics, University of Cambridge, Hills Road, Cambridge, U.K.; the ³Institute of Metabolic Science, Cambridge University Hospitals NHS Foundation Trust, Cambridge, U.K.; the ⁴Diabetes Centre, Ipswich Hospital NHS Trust, Ipswich, U.K.; and the ⁵Elsie Bertram Diabetes Centre, Norfolk and Norwich University Hospital NHS Trust, Norwich, U.K.

Corresponding author: Helen R. Murphy, hm386@medschl.cam.ac.uk.

Received 17 September 2010 and accepted 27 October 2010.

DOI: 10.2337/dc10-1796. Clinical trial reg. no. ISRCTN62568875, isrctn.org.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-1796/-DC1>.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

and capillary glucose levels during pregnancy (15,19). No studies have evaluated sensor accuracy with plasma glucose measurements during pregnancy.

Before outpatient closed-loop studies can proceed, they must be supported by scientifically rigorous data on the safety and efficacy of the real-time CGM and the control algorithm to function throughout the physiologic changes of pregnancy. The aim of this study was to evaluate the performance of the FreeStyle Navigator CGM and MPC control algorithm during early (12–16 weeks) and late gestation (28–32 weeks).

RESEARCH DESIGN AND METHODS

Study protocols were approved by the research ethics committee, and participants provided written informed consent.

Participants

From March 2009 to March 2010, 10 pregnant women with type 1 diabetes from three U.K. antenatal diabetes clinics (Cambridge $n = 7$, Norwich $n = 2$, and Ipswich $n = 1$) were recruited into studies to develop closed-loop systems for use in pregnancy. Inclusion criteria were type 1 diabetes (World Health Organization criteria) for at least 12 months before pregnancy, intensive insulin therapy (multiple daily injections or pump), and a viable singleton pregnancy with gestational age confirmed by ultrasound imaging. Women with poor glycemic control (A1C $>10\%$), significant obesity (BMI $\geq 35 \text{ kg/m}^2$), insulin resistance (total daily insulin dose $\geq 1.5 \text{ units/kg}$), nephropathy, autonomic neuropathy, or gastroparesis were excluded.

Study protocol

All participants were admitted to the Wellcome Trust Clinical Research Facility (Cambridge, U.K.) for 24 h on two occasions: once during early pregnancy (12–16 weeks) and again during later pregnancy (28–32 weeks).

Study devices and procedures

The day before each study, a FreeStyle Navigator sensor with a 10-h run-in calibration period (Abbott Diabetes Care, Alameda, CA) was inserted into the upper arm and calibrated with capillary glucose measurements according to the manufacturer's instructions. For five women who required multiple daily injections, basal insulin was withdrawn 24 h before admission and replaced with

rapid-acting insulin aspart (Novo Nordisk, Bagsvaerd, Denmark).

Patients arrived at the research facility at 1300 h and an intravenous sampling cannula was inserted. Women were connected to an insulin pump (Deltac Cozmo, Smiths Medical, St. Paul, MN) delivering insulin aspart. From 1400 h, venous samples were obtained every 15 min for plasma glucose concentration measured by the Yellow Springs Instrument analyzer (YSI2300 STAT Plus Analyzer, Farnborough, U.K.). At 1800 h, women ate a standardized evening meal of pasta with tomato-based vegetable sauce (602 Kcal, 80 g carbohydrate [50%], 9 g protein [31%], 4 g fat [15%]). They fasted overnight and ate a standardized breakfast of orange juice and toast with jam (356 Kcal; 60 g carbohydrate [60%], 11 g fat [28%], 7.6 g protein [8%])

at 0700 h the following morning. Prandial insulin doses were calculated according to the women's insulin/carbohydrate ratio and capillary glucose levels. The study ended at 1200 h.

MPC algorithm

The MPC algorithm calculated the basal insulin infusion rates. It was manually adjusted at 15-min intervals by a research nurse from 1400 to 1200 h the following day. It was initialized using women's weight, basal insulin requirements, and total daily insulin dose during the preceding 3 days. For women who required multiple daily injections, the total daily insulin dose was reduced by 30% for conversion to pump therapy.

Sensor glucose measurements were used to update two model parameters: an endogenous glucose flux correcting for

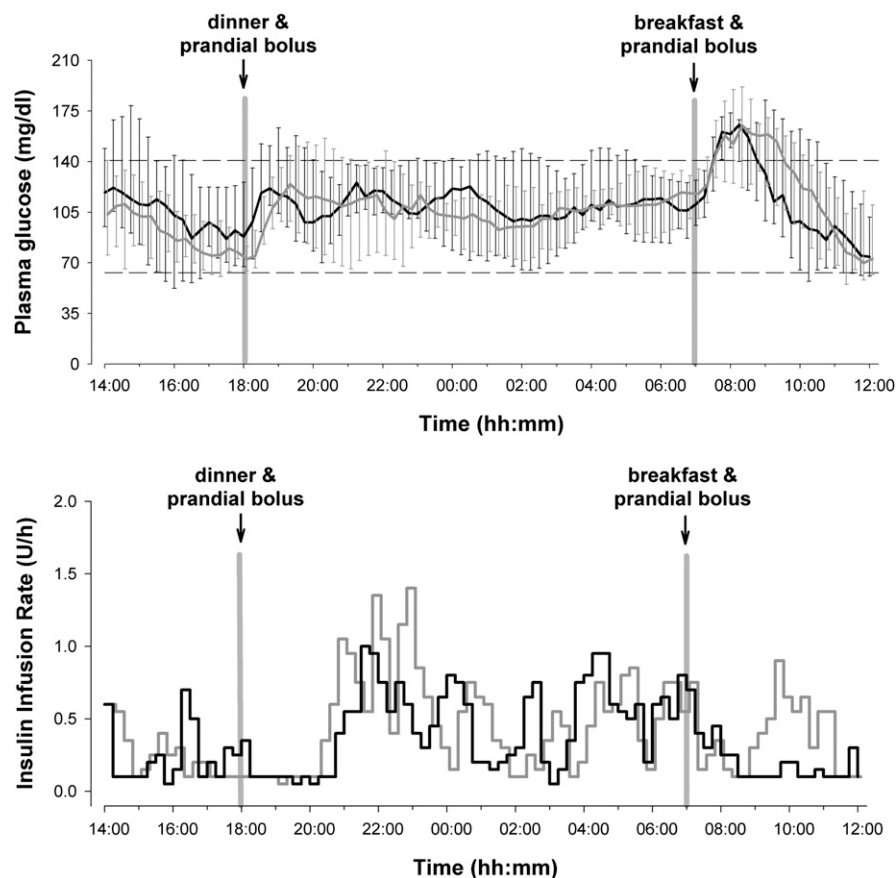


Figure 1—Plasma glucose concentrations and insulin infusion rates are shown during early and late gestation. The dark lines represent the median plasma glucose levels and insulin infusion rates during early pregnancy (visit 1, 14.8 weeks) and the lighter lines during late pregnancy (visit 2, 28.0 weeks). On both visits, a standardized dinner (80 g carbohydrate) was eaten at 1800, followed by an overnight fast until breakfast (60 g carbohydrate) at 0700 h the next morning. Prandial insulin boluses were calculated according to the women's insulin-carbohydrate ratio and capillary fingerstick glucose levels. Basal insulin infusion rates were calculated using CGM sensor glucose values and the MPC algorithm.

errors in model-based predictions and carbohydrate bioavailability. Several competing models differing in the rates of subcutaneous insulin absorption and carbohydrate absorption were run in parallel. A combined model forecasted plasma glucose excursions over a 2.5-h prediction horizon. Infusion rates were calculated to achieve a sensor glucose target of 104.4 mg/dL, with safety rules including a predefined maximal basal insulin infusion rate to prevent overdosing and flexibility to increase the target to 131.4 mg/dL if previous predictions were inaccurate. Plasma glucose levels were available for safety purposes, but only sensor glucose levels were fed into the algorithm.

Statistical analysis

Power calculations were not performed because this was an exploratory safety study. The sample size was pragmatic, based on data in human pregnancy, documenting increased gestational gluconeogenesis in seven women (16). Mean glucose, time spent in target (National Institute for Health and Clinical Excellence recommended range, 63–140 mg/dL) (20), time spent below target (<63 and ≤50 mg/dL), time spent above target (>140 and ≥180 mg/dL), and insulin infusion rate were calculated for each visit using plasma and sensor glucose measurements. Glucose control measures were calculated from 1800 h, reflecting that it takes 4 h for closed-loop to become effective.

Because many variables were not normally distributed, the Wilcoxon non-parametric test was used to compare the two study periods. Separate analyses were conducted of the periods after dinner (1800–2300 h), overnight (2300–0700 h), and after breakfast (0700–1200 h). Values are given as median (interquartile range).

Linear mixed-effects models were applied to the glucose measurements. Participants were treated as random effects, and gestational age (early or late pregnancy), time of day (after dinner, overnight, after breakfast) as fixed effects. The correlation structure of repeated glucose measurements within each study was modeled using a Box-Jenkins model with two parameters for the autocorrelation and two parameters for the moving average; namely, an autoregressive moving average (2,2) model. Maximum likelihood algorithms were used to estimate parameters. The hypothesis of interest was whether glucose levels showed systematic differences between early and late

pregnancy across subjects, tested with likelihood ratio tests. Analyses were conducted on SPSS v15 software (SPSS Inc., Chicago, IL) and on R v2 11.1 (Free Software Foundation, Boston, MA).

Sensor accuracy was evaluated throughout the study (1400–1200 h) as the relative absolute difference between sensor glucose and paired plasma glucose divided by plasma glucose and by Clarke error-grid analysis (21). Grade “A+B” assessed sensor efficacy and grade “D+E” assessed sensor safety. Low blood glucose index was calculated as an average of transformed glucose measurements progressively increasing at low glucose levels and assessed the duration and extent of hypoglycemia.

RESULTS—Participants were a median (interquartile range) age of 31.1 (28.7–31.7) years, had a diabetes duration of 19 (13.5–24) years, a weight of 66.6 (64–73.9) kg, a booking A1C of 6.9% (6.2–8.0), and a BMI of 24.1 (23.1–26.3) kg/m². Individual characteristics and gestational changes in A1C, weight, and insulin doses are shown in the Supplementary Data. Comparing the early (14.8 weeks) and late (28.0 weeks) gestation visits, there were no significant differences between plasma glucose levels (in mg/dL) at study commencement (118.8 [95.4–156.6] and 102.6 [75.6–140.4; P = 0.5]), or throughout the study

(117 [100.8–154.8] and 126 [109.8–140.4; P = 0.72]). Plasma glucose levels and insulin infusion rates are shown in Fig. 1.

Comparison of overnight glucose control in early and late pregnancy

The level of overnight glucose control achieved during closed-loop insulin delivery is summarized in Table 1. The time spent with plasma glucose level within the target of 63 to 140 mg/dL was 84% (50–100%) in early pregnancy and 100% (94–100%) in late pregnancy (P = 0.09). Differences between time spent below target (<63 or ≤50 mg/dL) during early and late pregnancy were not statistically significant. There were no episodes of symptomatic nocturnal hypoglycemia. There was one episode of unexplained hypoglycemia documented as CGM glucose of 63 mg/dL and plasma glucose of 46.8 mg/dL at 0500 h in early pregnancy, despite an infusion of only 0.4 units of basal insulin during the preceding 6 h (0.066 units/h).

The time spent hyperglycemic (>140 mg/dL) was 7% (0–40%) in early pregnancy and 0% (0–6%) in late pregnancy (P = 0.25). There were no overnight episodes of hyperglycemia ≥180 mg/dL. Glucose variability assessed by the standard deviation of plasma glucose was unchanged, as was the mean insulin infusion rate and standard deviation of the insulin infusion in early and late pregnancy.

Table 1—Overnight glucose control using FreeStyle Navigator continuous glucose monitor and the MPC algorithm in women with type 1 diabetes during early and late pregnancy

Variable	Early pregnancy	Late pregnancy	P value
Median plasma glucose, mg/dL			
At start of night (2300 h)	102.6 (100.8–142.2)	113.4 (86.4–122.4)	0.51
Overnight (2300–0700 h)	109.8 (82.8–131.4)	109.8 (99–113.4)	0.57
SD overnight plasma glucose	14.4 (10.8–21.6)	16.2 (12.6–23.4)	0.28
Time in target (63–140 mg/dL), %	84 (50–100)	100 (94–100)	0.09
Nocturnal hypoglycemia			
% Time hypoglycemic <63 mg/dL	0 (0–3)	0 (0–0)	0.18
% Time hypoglycemic ≤50 mg/dL*	0 (0–0)	0 (0–0)	0.32
Nocturnal hyperglycemia			
% Time hyperglycemic >140 mg/dL	7 (0–40)	0 (0–6)	0.25
% Time hyperglycemic ≥180 mg/dL	0 (0–0)	0 (0–0)	0.32
Blood glucose index			
Low	0.9 (0.0–4.3)	1.1 (0.2–2.7)	0.80
High	0.3 (0.0–1.3)	0.2 (0.1–0.5)	0.51
Mean insulin infusion, units/kg	0.5 (0.4–0.8)	0.6 (0.4–1.1)	0.80
SD insulin infusion rate	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.11

Values are given as median (interquartile range). *There was one episode of unexplained nocturnal hypoglycemia in early pregnancy (CGM glucose 63 mg/dL, plasma glucose 46.8 mg/dL) at 0500 h despite only 0.4 units of basal insulin infused during the preceding 6 h (insulin infusion rate 0.066 units/h).

There was no difference in the level of glucose control achieved by women using insulin pumps or multiple daily injections (data not shown).

Postprandial glucose control in early and late pregnancy

There were no differences in the pre- and postprandial glucose levels for the evening meal or breakfast in early and late pregnancy (Table 2). After 4 h of closed-loop insulin delivery, plasma glucose levels were 88.2 (68.4–127.8) mg/dL in early and 73.8 (64.8–82.8) mg/dL in late pregnancy ($P = 0.14$). After a large evening meal (80 g carbohydrate), for which women decided their own prandial insulin dose, the time spent with plasma

glucose levels in target was 68% (61–97%) in early and 77% (58–93%) in late pregnancy ($P = 0.51$). There were no significant changes in the time spent hypoglycemic or hyperglycemic, with 13% (0–39%) time spent hyperglycemic in early pregnancy compared with 5% (0–41%) in late pregnancy ($P = 0.24$).

The fasting plasma glucose levels were 109.8 (95.4–126) mg/dL and 118.8 (102.6–133.2) mg/dL in early and late pregnancy ($P = 0.14$). After a 60-g carbohydrate breakfast, the postprandial glucose levels, time in target, glucose variability, and insulin infusion rates and variability were not statistically different in early or late gestation. However, less time was spent with plasma glucose

within the target range after breakfast—59% (40–74%) early and 47% (39–77%) late pregnancy—and more time spent hyperglycemic after breakfast—28% (20–58%) early and 44% (10–55%) late pregnancy—compared with the after dinner or overnight periods.

CGM sensor accuracy

Sensor accuracy, evaluated as the mean absolute relative difference between sensor glucose and paired plasma glucose divided by plasma glucose, was 13.3% (14.7% in early vs. 11.9% in late pregnancy; $P = 0.15$). Median absolute relative differences were 11.4% (12.8% in early vs. 9.9% in late pregnancy; $P = 0.21$). According to Clarke error grid analysis (EGA), 93.6% values in early and 95.6% in late pregnancy were clinically acceptable (zones A + B), with no overcorrection errors or unsafe control (Table 3).

CONCLUSIONS—Here we demonstrate clinically and statistically acceptable accuracy of the FreeStyle Navigator CGM and MPC algorithm in women with type 1 diabetes during pregnancy. Closed-loop insulin delivery was associated with nearly normoglycemia overnight, both in early and in late pregnancy, suggesting that the MPC algorithm safely adapts insulin delivery for advancing gestational age.

Sensing errors have been considered a major obstacle to effective closed-loop systems. This represents a particular challenge given the narrow glucose reference range and risk of hypoglycemia during pregnancy. Despite tighter glycemic targets, sensor accuracy in this study was comparable to previously published data (19). As in nonpregnant individuals, accuracy was greatest for glucose levels within and above the target range and least for glucose levels ≤ 70 mg/dL. The MPC algorithm compensated for discrepancies between the sensor and reference glucose level during hypoglycemia by suspending insulin delivery when sensor glucose values fell < 80 mg/dL.

Despite this safety barrier, there was one episode of unexplained asymptomatic hypoglycemia at 0500 h, which could not be attributed to sensor discrepancy or to the MPC advice, because only 0.4 units of insulin was infused over the preceding 6 h. Considered in the context of conventional treatment, whereby women with type 1 diabetes spend on average 16.2% overnight (1.3 h) hypoglycemic during pregnancy (2) and assuming this

Table 2—Pre- and postprandial glucose control with prandial insulin boluses calculated by women according to insulin/carbohydrate ratio and fingerstick glucose values

Variable	Early pregnancy	Late pregnancy	P value
Before and after 80-g carbohydrate evening meal			
Plasma glucose at start (1400 h), mg/dL	118.8 (95.4–149.4)	102.6 (75.6–140.4)	0.5
Plasma glucose pre-evening meal (1800 h), mg/dL	88.2 (68.4–127.8)	73.8 (64.8–82.8)	0.14
Median postprandial plasma glucose (1800–2300 h), mg/dL	104.4 (100.8–136.8)	108 (82.8–135)	0.20
SD plasma glucose	25.2 (14.4–32.4)	19.8 (18–25.2)	0.24
% Time in target (63–140 mg/dL)	68 (61–97)	77 (58–93)	0.51
% Time hypoglycemic < 63 mg/dL	0 (0–8)	3 (0–18)	0.46
% Time hypoglycemic < 50 mg/dL	0 (0–0)	0 (0–0)	0.65
% Time hyperglycemic > 140 mg/dL	13 (0–39)	5 (0–41)	0.24
% Time hyperglycemic > 180 mg/dL	0 (0–2)	0 (0–0)	0.18
Blood glucose index			
Low	1.2 (0.1–2.0)	1.2 (0.5–6.3)	0.44
High	0.7 (0.0–2.2)	0.3 (0.0–1.7)	0.17
Mean insulin infusion, units/kg	0.5 (0.3–0.6)	0.6 (0.2–0.9)	0.96
SD insulin infusion rate	0.5 (0.4–0.7)	0.6 (0.4–0.9)	0.72
Before and after 60-g carbohydrate breakfast			
Fasting plasma glucose (0700 h)	109.8 (95.4–126)	118.8 (102.6–133.2)	0.14
Median postprandial plasma glucose (0700–1200 h), mg/dL	117 (100.8–154.8)	126 (109.8–140.4)	0.72
SD plasma glucose	32.4 (18.0–41.4)	34.2 (21.6–48.6)	0.80
% Time in target (63–140 mg/dL)	59 (40–74)	47 (39–77)	0.88
% Time hypoglycemic < 63 mg/dL	1 (0–23)	1 (0–18)	1.0
% Time hypoglycemic < 50 mg/dL	0 (0–0)	0 (0–1)	0.18
% Time hyperglycemic > 140 mg/dL	28 (20–58)	44 (10–55)	0.86
% Time hyperglycemic > 180 mg/dL	0 (0–25)	3 (0–24)	0.83
Blood glucose index			
Low	1.2 (0.2–5.5)	1.5 (0.1–3.7)	0.80
High	1.2 (0.8–5.6)	2.1 (0.4–4.3)	0.96
Mean insulin infusion, units/kg	0.3 (0.2–0.9)	0.5 (0.3–1.0)	0.24
SD insulin infusion rate	0.7 (0.2–1.0)	0.5 (0.1–1.3)	0.88

Values are given as median (interquartile range).

Table 3—Accuracy of FreeStyle Navigator continuous glucose monitor during early and late pregnancy

Measure	Overall	Early pregnancy	Late pregnancy	P value
Data points	1,923	966	957	
Target range (70–180 mg/dL)	1,609	794	815	
Hypoglycemia (<70 mg/dL)	247	132	115	
Hyperglycemia (>180 mg/dL)	67	40	27	
Mean absolute relative difference (%)				
Overall	13.3	14.68	11.93	0.15
Target range	12.16	13.44	10.92	
Hypoglycemia	21.91	23.70	19.84	
Hyperglycemia	9.25	9.52	8.86	
Median absolute relative difference (%)				
Overall	11.42	12.85	9.89	0.21
Target range	10.46	12.07	8.99	
Hypoglycemia	21.58	22.75	20.33	
Hyperglycemia	9.06	9.27	8.73	
International Standards Organization criteria*				
Overall	79.62	76.40	82.86	0.33
Target range	81.54	78.21	84.79	
Hypoglycemia	61.94	58.33	66.09	
Hyperglycemia	98.51	100	96.30	
Error grid analysis, %				
A—Clinically accurate	78.94	75.75	82.45	0.55†
B—Within 20% of reference	15.70	17.90	13.17	
C—Overcorrection error	0	0	0	
D—Failure to detect hypoglycemic or hyperglycemic excursion	5.36	6.35	4.39	
E—Unsafe control	0	0	0	

*International Standards Organization criteria are based on the percentage CGM measurements within 15 mg/dL from reference when the reference plasma glucose is ≤ 75 mg/dL or within 20% from reference when the reference plasma glucose is > 75 mg/dL. †P value refers to error grid analysis A + B combined values of 93.6% in early pregnancy vs. 95.6% in late pregnancy.

group of women were representative, it suggests potential safety benefits of closed-loop insulin delivery. Note that in this proof of concept study, we did not modify the algorithm to distinguish between pre- and postprandial glucose targets and that even tighter glycemic thresholds (60–99 fasting and < 130 after meals) may be required for optimal fetal growth.

Nocturnal hyperglycemia was minimized in women requiring established continuous subcutaneous insulin infusion as well as in those using multiple daily injections. This also compares favorably with previous CGM studies describing 36.4% time hyperglycemic (2.9 h > 140 , 1.0 h > 200 mg/dL) (2).

The level of overnight glucose control obtained during early and late gestation was similar to that recently obtained in children and adults with type 1 diabetes (18). Our group has shown that using off-the-shelf sensors and earlier versions of this MPC algorithm, children achieved

53% (48–57%) overnight time in target after eating a large, rapidly absorbed evening meal and 55% (37–64%) after a large, slowly absorbed meal (18). Adults using closed-loop did even better, spending $72 \pm 15\%$ overnight time in target after a large evening meal (100 g carbohydrate) and generous alcohol consumption (0.75 g/kg ethanol) (22). These studies suggest potential superiority of overnight closed-loop insulin delivery over conventional pump therapy outside pregnancy.

The difference between conventional and close-loop insulin delivery is the ability of the latter to rapidly respond to glucose excursions, with more variability of the insulin infusion rates despite comparable overall insulin doses. In our current study, the MPC algorithm was able to safely increase the insulin infusion rates for advancing gestational age, based on the women's weight and total daily insulin dose.

This study also illustrates the challenges of postprandial hyperglycemia,

particularly after a high-carbohydrate breakfast. After nearly optimal overnight control, women had more glucose variability and spent more time hyperglycemic after breakfast compared with after dinner. Despite apparently more prolonged hyperglycemia after breakfast in late pregnancy (Fig. 1), differences in the time spent hyperglycemic between early and late pregnancy (28% in early and 44% in late gestation) did not reach statistical significance, most likely due to the small sample size and intraindividual variability.

There were also no significant differences in the insulin infusion rates (when corrected for maternal weight) in early and late gestation. However, there is a trend to higher glucose levels at various points in later pregnancy, after starting at a lower glucose, and a trend to an increased average insulin infusion rate. The latter would be expected given the increasing insulin resistance of pregnancy and with larger numbers may have reached statistical significance.

We now plan to perform randomized controlled studies of closed-loop insulin delivery with tighter glycemic targets, first in the hospital and then over multiple nights in the home setting. To evaluate clinical effectiveness of closed-loop insulin delivery, a large, multicenter randomized study comparing closed-loop with sensor-augmented pump therapy will be needed. Meanwhile, the MPC safety and sensor accuracy data from this study pave the way for future research to refine closed-loop insulin delivery in pregnancy.

Acknowledgments—This study was supported by Diabetes UK Project Grant BDA 07/003551. H.R.M. was funded by National Institute for Health Research (NIHR) research fellowship (PDF/08/01/036). This study was also supported by JDRF, Abbott Diabetes Care (FreeStyle Navigator CGM and sensors free of charge), Medical Research Council, Centre for Obesity and Related Metabolic Diseases, NIHR, Cambridge Biomedical Research Centre, and Addenbrooke's Wellcome Trust Clinical Research Facility.

H.R.M. has received speaker honoraria from Minimed Medtronic. R.H. has received speaker honoraria from Minimed Medtronic, LifeScan, and Novo Nordisk and serves on the Animas advisory panel. R.H. and M.E.W. receive license fees from Becton Dickinson and have filed patent applications. No other potential conflicts of interest relevant to this article were reported.

H.R.M., R.T., and R.H. designed the study. J.M.A., J.H., D.S., R.T., and G.R. recruited participants. J.M.A., J.H., D.E., and H.R.M.

performed studies. A.H. and M.N. analyzed data. H.R.M., M.N., and R.H. interpreted data. H.R.M. drafted the manuscript. R.T., D.E., M.E.W., D.S., D.B.D., and R.H. reviewed and edited the manuscript. All authors approved the final version.

Interim data from this study (confined only to findings in early pregnancy) were presented at the American Diabetes Association (26 June 2010), Diabetes UK (3 March 2010), and Advanced Technologies and Treatments for Diabetes (12 February 2010) meetings.

References

- García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. *Diabetologia* 2010;53:446–451
- Murphy HR, Rayman G, Duffield K, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. *Diabetes Care* 2007;30:2785–2791
- 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;328:915–920
- Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ* 2006;333:177–262
- Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. *Diabetes Care* 2010;33:2514–2520
- Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. *Diabetes Care* 2009;32:2005–2009
- Tripathi A, Rankin J, Aarvold J, Chandler C, Bell R. Preconception counseling in women with diabetes: a population-based study in the north of England. *Diabetes Care* 2010;33:586–588
- Torlone E, Di Cianni G, Mannino D, Lapolla A. Insulin analogs and pregnancy: an update. *Acta Diabetol* 2009;46:163–172
- Chen R, Ben-Haroush A, Weissman-Brenner A, Melamed N, Hod M, Yogeve Y. Level of glycemic control and pregnancy outcome in type 1 diabetes: a comparison between multiple daily insulin injections and continuous subcutaneous insulin infusions. *Am J Obstet Gynecol* 2007;197:e401–e405
- Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
- Bergental RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311–320
- Pickup JC, Hammond P. NICE guidance on continuous subcutaneous insulin infusion 2008: review of the technology appraisal guidance. *Diabet Med* 2009;26:1–4
- Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ* 2008;337:a1680
- Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and meta-analysis of randomized, controlled trials. *Am J Obstet Gynecol* 2007;197:447–456
- Chitayat L, Zisser H, Jovanovic L. Continuous glucose monitoring during pregnancy. *Diabetes Technol Ther* 2009;11(Suppl. 1):S105–S111
- Kalhan S, Rossi K, Gruca L, Burkett E, O'Brien A. Glucose turnover and gluconeogenesis in human pregnancy. *J Clin Invest* 1997;100:1775–1781
- Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med* 2006;23:1–12
- Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010;375:743–751
- Clarke WL, Kovatchev B. Continuous glucose sensors: continuing questions about clinical accuracy. *J Diabetes Sci Tech* 2007;1:669–675
- NICE guideline 63: Diabetes in pregnancy. Management of diabetes and its complications from the pre-conception to the postnatal period [article online]. Available from www.nice.org. 2008. Accessed 26 March 2008
- Clarke WL. The original Clarke error grid analysis (EGA). *Diabetes Technol Ther* 2005;7:776–779
- Kumareswaran K, Harris J, Elleri D, et al. Overnight closed loop (CL) glucose control following consumption of alcohol in adults with type 1 diabetes. *Diabetes* 2010;59(Suppl. 1):A95