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A Diabetes Pregnancy Technology Roadmap: The 2023 Norbert Freinkel Award Lecture

Helen R. Murphy

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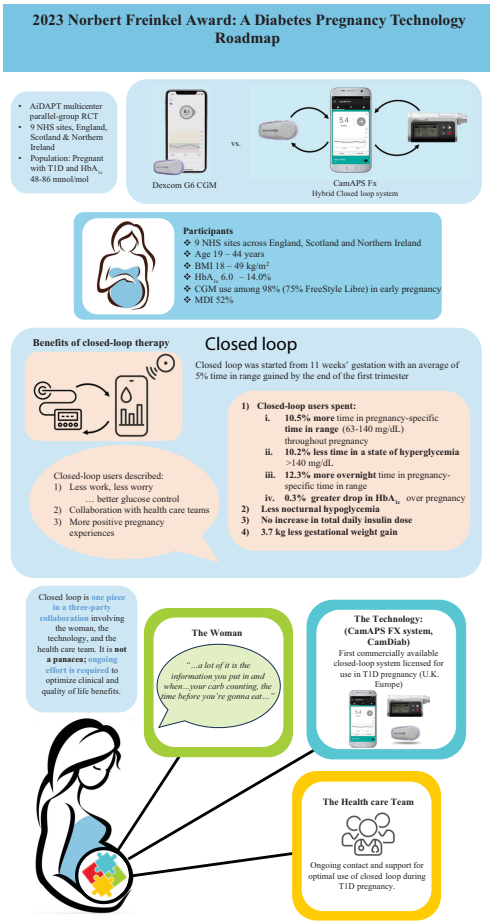

AiDAPT, Automated insulin Delivery Amongst Pregnant women with Type 1 diabetes; CGM, continuous glucose monitor; MDI, multiple daily injections; NHS, National Health Service; RCT, randomized controlled trial; T1D, type 1 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Norbert Freinkel emphasized the need for "more aggressive therapy with exogenous insulin" during type 1 diabetes (T1D) pregnancy.
- **What is the specific question we wanted to answer?**
  Can the use of hybrid closed loop (HCL) therapy compared with exogenous insulin therapy with continuous glucose monitoring improve maternal glucose levels throughout T1D pregnancy?
- **What did we find?**
  Use of HCL was associated with 10.5% more time in the pregnancy-specific target glucose range (63–140 mg/dL) from 16 weeks' gestation until delivery and 3.7 kg less gestational weight gain, with more positive pregnancy experiences, in a representative patient population.
- **What are the implications of our findings?**
  Use of a pregnancy-specific HCL system should be offered to all pregnant women with T1D, starting from before pregnancy, where possible.

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ADA AWARD LECTURE

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Norbert Freinkel emphasized the need for "more aggressive therapy with exogenous insulin" during type 1 diabetes (T1D) pregnancy. Recent advances in diabetes technology, continuous glucose monitoring (CGM), and hybrid closed-loop (HCL) insulin delivery systems allow us to revisit Freinkel's observations from a contemporary perspective. The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) led to international recommendations that CGM be offered to all pregnant women with T1D to help them meet their pregnancy glucose targets and improve neonatal outcomes. However, despite CGM use, only 35% of trial participants reached the pregnancy glucose targets by 35 weeks' gestation, which is too late for optimal obstetric and neonatal outcomes. The constant vigilance to CGM data and insulin dose adjustment, with perpetual worry about the impact of hyperglycemia on the developing fetal structures, leave many pregnant women feeling overwhelmed. HCL systems that can adapt to marked gestational changes in insulin sensitivity and pharmacokinetics may help to bridge the gap between the nonpregnant time in range glycemic targets (70–180 mg/dL) and the substantially more stringent pregnancy-specific targets (TIRp) (63–140 mg/dL) required for optimal obstetric and neonatal outcomes. Use of HCL (CamAPS FX system) was associated with a 10.5% higher TIRp, 10.2% less hyperglycemia, and 12.3% higher overnight TIRp. Clinical benefits were accompanied by 3.7 kg (8 lb) less gestational weight gain and consistently achieved across a representative patient population of insulin pump or injection users, across trial sites, and across maternal HbA_{1c} categories. Working collaboratively, women, HCL technology, and health care teams achieved improved glycemia with less worry, less work, and more positive pregnancy experiences.

In his 1980 Banting lecture, "Of Pregnancy and Progeny," Norbert Freinkel made poignant observations that provide a compelling basis for "more aggressive therapy with exogenous insulin" (1). His beautifully articulated lecture deserves to be read in its entirety, and if some time has elapsed since its first reading, it warrants rereading. Freinkel elaborates on the seminal discoveries, as pertinent to clinicians and researchers focused on the gestational challenges of managing diabetes during pregnancy currently, as they were five decades ago. Recent advances in diabetes technology, continuous glucose monitoring (CGM) and automated hybrid closed-loop (HCL) insulin delivery systems, allow us to revisit Freinkel's observations from a contemporary perspective.

It is a great honor to be the third Irish, and ninth female, recipient of the Norbert Freinkel Award. I studied medicine at University College Dublin, which dates its origin from the foundation of the Catholic University of Ireland in 1851. The teaching of medicine commenced in 1855, with clinical attachments at the Mater Misericordia hospital, which aimed to provide "the best in medical care to all those who needed

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it - irrespective of their means." The first medical specialist obstetric physician was appointed in 1878, with University College Dublin undergraduates earning bachelor's degrees in medicine, surgery, and obstetrics (MB BCh BAO). With heavily subsidized university fees, my summers were spent exploring wider interests, including overseas electives in research and developing obstetrical skills, at a remote mission hospital on the edge of the Zambezi valley, in Zambia. I combined postgraduate endocrinology training with travels to New Zealand, before spending a year in Adelaide, Australia, where my interest in diabetes pregnancy began. Adelaide was home to the randomized controlled trial Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), which established the importance of detecting and managing gestational diabetes mellitus (2).

Returning to the U.K. with two young children, my MD thesis (by dissertation) focused on diabetes self-management education and teamwork between children and young people and families affected by type 1 diabetes (T1D) (3–5). The lived experiences of children and young people, navigating daily glucose excursions using multiple daily injections, which Freinkel described as the Alps "rather than the gentle foothills of the Berskshires," with painful self-monitoring of capillary blood glucose (SMBG), stimulated my early interest in CGM.

CGM: "A STEPPING STONE IN THE JOURNEY TOWARD A CURE"

In 2005, David Klonoff described the attractive features of available and likely soon to be available CGM systems, measuring glucose in interstitial fluid rather than blood (6). These were hailed by the late Lois Jovanovic, the first female recipient of the Norbert Freinkel award, as a "stepping stone in the journey toward a cure" (7). These reviews stimulated my early interest in exploring the role of CGM technology in pregnancy. Using the first commercially available CGM system, we had the technology to quantify fetal exposure to maternal hyperglycemia in unprecedented detail. These early retrospective CGM profiles confirmed the frequency and duration of postprandial hyperglycemia, or "heightened metabolic oscillations during the shuttlings from fed to fasted state," as eloquently expressed by Norbert Freinkel (1).

In our first study, 40 pregnant women with T1D wore masked CGM sensors (Medtronic Continuous Glucose Monitoring System Gold) for 1 week in each trimester (8). These women who were pioneers of early CGM use helped us to demonstrate that despite near-optimal glycemic control, according to HbA_{1c} (6.7%, 6.4%, and 5.9% during the first, second, and third trimester, respectively), the percentage of time spent with glucose levels between 70 and 140 mg/dL was 40% (10 h/day) in early pregnancy. Furthermore, while maternal hyperglycemia decreased across gestation, time spent with levels $>$140 mg/dL was 33% (8 h/day) during the third trimester (8). Despite the many limitations of early CGM technology (masked, no mobile phone compatibility, no alarms for out-of-range values, limited accuracy at lower glucose range, not waterproof, not suitable for wearing on the arm), we demonstrated that pregnant women using CGM in addition to capillary blood glucose monitoring had lower HbA_{1c} in late pregnancy (9). As noted by Norbert Freinkel, "the developing fetal structures exquisitely are attuned to fine alterations in maternal fuel economy." Hence, these small changes in maternal glucose, most likely attributed to changes in maternal diet and insulin therapy adjustments, were associated with lower birth weight SD scores and reduced the incidence of large for gestational age in our initial randomized controlled study (9).

INSIGHTS FROM CONCEPTT

With subsequent advances in CGM technology, two further randomized studies were conducted during pregnancy. A Danish study using a newer CGM with alarms for out-of-range values found no clinical advantage associated with intermittent use of real-time CGM, most likely related to intermittent rather than continuous CGM use (10). A larger study from the Netherlands using masked CGM sensors intermittently also reported disappointing results (11). Hence, the international multicenter Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT), which I co-led together with Professor Denice Feig, University of Toronto, sought to provide definitive data on the role of real-time CGM use, as compared with SMBG, before and during T1D pregnancy (12). CONCEPTT unequivocally established the benefits of using real-time CGM continuously from early pregnancy until delivery (13). By 34–35 weeks' gestation, pregnant women assigned to CGM spent more time in the pregnancy-specific glucose target range (TIRp) of 63–140 mg/dL (68%) in comparison with those assigned to SMBG use (TIRp 61%) (13).

In keeping with results from our own initial randomized study, and Freinkel's hypothesis regarding the developing fetal structures being exquisitely sensitive to small changes in maternal glucose, for the neonatal offspring of CONCEPTT mothers assigned to CGM there were lower rates of large-for-gestational-age birth weight and there was less neonatal hypoglycemia accompanied by fewer and shorter stays in the neonatal intensive care unit. The numbers needed to treat were small (six mothers to prevent one neonatal intensive care unit admission), meaning that CGM use was both clinically effective and cost-effective during T1D pregnancy. The CGM treatment effect was comparable across international sites (with varying CGM technology experience) and independent of maternal insulin delivery method, meaning that the results were generalizable and applicable to women using multiple daily injections and insulin pump therapy (13). These data led to changes in clinical guidelines, with the U.K. National Institute for Health and Care Excellence (NICE) recommending that real-time CGM be offered to all pregnant women with T1D, to help them meet their pregnancy glucose targets and improve neonatal outcomes (14).

In the U.K., CGM was reimbursed by the National Health Service, meaning that real-time CGM technology was available to all those who needed it, irrespective of their means. During 2022, 5 years following CONCEPTT, data from the National Pregnancy in Diabetes (NPID) Audit demonstrated that $<$5% of pregnant women in the U.K. were using SMBG alone. These data confirm that widespread use of CGM has transformed the management of diabetes during pregnancy, with improved maternal glucose before and during pregnancy associated with reductions in congenital anomaly and perinatal deaths, collectively serious adverse pregnancy outcomes, in addition to the benefits for obstetric and neonatal complications—as expected from CONCEPTT. However, data from the T1D Exchange in the U.S. highlight concerning racial, ethnic, and socioeconomic disparities in CGM access with regard to those of

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younger age, lower income, lower educational attainment, female sex, and Non-Hispanic Black and Hispanic race and ethnicity, e.g., those most at risk for serious adverse pregnancy outcomes but least likely to have had access to it during 2015–2018 (15). More work is needed to reduce health care inequalities and improve access to diabetes technology worldwide.

However, it is clear that CGM alone will not be adequate for most women to achieve and maintain optimal glucose levels throughout T1D pregnancy. Secondary analyses from CONCEPTT demonstrated that 10% of participants archived the recommended 70% TIRp during the first and second trimesters (16), only rising to 35% by 35 weeks' gestation (17). Furthermore, participants using multiple daily injections had more favorable second-trimester glycemia (5% higher TiRp) than those using insulin pump therapy (18). Hence, in parallel with the rigorous evaluation of existing diabetes technology, we have focused on the development of HCL systems to facilitate "more aggressive therapy with exogenous insulin," as outlined by Freinkel. We began by examining CGM accuracy during pregnancy, specifically to understand whether the gestational changes in maternal physiology impacted on the measurement of glucose in interstitial fluid. Sensor accuracy was comparable during early and late pregnancy and, indeed, no different from accuracy reported outside of pregnancy (19).

CARBOHYDRATE METABOLISM AND INSULIN ABSORPTION DURING T1D PREGNANCY

Freinkel noted that "pregnancy changes the metabolism of every class of foodstuff." We explored the gestational impact of carbohydrate metabolism, using HCL therapy to stabilize maternal glucose and stable label isotope tracers ([6,6-(2)H(2)]glucose and [U-(13)C]glucose), to quantify systemic glucose appearance, disposal, and bioavailability. We found that the appearance of glucose from ingested carbohydrate into the maternal circulation did not change from early to late pregnancy following a standardized sugar-rich breakfast (60 g carbohydrate) and a starch-rich dinner (80 g carbohydrate) (20).

However, by 28–32 weeks' gestation the disposal of systemic glucose was markedly delayed, leading to more prolonged postprandial hyperglycemia after both meals. Additionally, it took almost 20 min longer for insulin to reach maximal concentrations, accompanied by significantly greater variability in plasma insulin absorption during late pregnancy (49 min [interquartile range 37–55] vs. 71 min [52–108]; P = 0.004). We also found differences in insulin aspart pharmacokinetics during late pregnancy (21). Insulin absorption was almost 50% slower at 38 weeks compared with 8 weeks of gestation in insulin pump therapy users (21). Between-patient variability is well recognized outside of pregnancy, but we found higher-than-expected *within-patient* variability, implying that most variability in insulin absorption is occasion specific rather than individual specific during late pregnancy (21–23). Physical activity was remarkably effective for speeding up insulin absorption, reducing the mean time to peak postprandial aspart concentration from 55 to 40 min, and for improving maternal glycemia, although (at that time) CGM sensor accuracy was also of concern during exercise (21,24,25).

These experimental data highlighting the physiological and pharmacokinetic challenges go some way toward explaining why even the most motivated women using existing CGM and insulin pump technologies may struggle to achieve and maintain the tight pregnancy-specific glucose targets throughout pregnancy. These frustrations, in addition to the worry about the impact of hyperglycemia on their babies and constant vigilance to insulin dose adjustment throughout pregnancy, can leave many women feeling overwhelmed by T1D management (26).

HCL THERAPY

Outside of pregnancy, use of HCL is associated with improved glycemic outcomes (both HbA_{1c} and CGM metrics) as well as improved patient-reported outcomes (27,28). Randomized controlled trials consistently demonstrate lower HbA_{1c} and higher percentage of time in range and quality of life benefits in children, young people, and adults with T1D (27,29–31). Data regarding HCL use in pregnancy were limited to feasibility studies or small case series involving off-label use of commercially available systems with higher glucose targets that may not be applicable during T1D pregnancy (32–34).

In advance of our pivotal Automated insulin Delivery Amongst Pregnant women with Type 1 diabetes (AiDAPT) randomized controlled trial, we performed four preliminary studies during pregnancy (two in hospital and two in home settings) using earlier versions of the Cambridge (CamAPS) algorithm. Firstly, we examined the feasibility of using an overnight HCL system to determine whether the model predictive control algorithm could adapt to gestational changes in insulin sensitivity. In 10 pregnant women (mean HbA_{1c} 6.9%), overnight median percent TIRp was 84% (interquartile range 50–100) in early and 100% (94–100) in late T1D pregnancy in a supervised clinical research facility setting (19). We then examined the feasibility of using HCL over 24 h in 12 pregnant women, all experienced insulin pump users (mean HbA_{1c} 6.4%). Participants were randomized to 24 h of HCL or CGM and standard insulin pump therapy on two occasions during mid-pregnancy (~20–24 weeks' gestation). They ate standardized meals and snacks and performed the same physical activities at both visits. TIRp was comparable between the insulin pump and closed-loop phases, 81% (59–87) vs. 81% (54–90), respectively, with less hypoglycemia during HCL therapy (35). Together, these studies facilitated regulatory approval to examine HCL use over longer durations in home settings (19,35).

We then performed two randomized crossover studies examining the use of a prototype HCL system (initially overnight and then over 24 h) over 4 weeks in home settings (36,37). Sixteen pregnant women (mean HbA_{1c} 6.8%) completed 28 days of HCL and 28 days of CGM with insulin pump therapy, in random order, separated by a 2- to 4-week washout period. The overnight median percent TIRp was increased from 60% during CGM with insulin pump therapy to 75% during HCL therapy (36). Because of the impact of overnight glycemia on 24-h glucose control, this corresponded to a 10% higher TIRp (56% vs. 66%) during HCL. Most participants (14 of 16) continued using HCL throughout pregnancy, spending 70% TIRp from 24 weeks' gestation, 77% TIRp from 34 weeks' gestation, and 87% TIRp during labor and birth. Participants expressed strong desire to continue HCL during their in-patient hospital admission for labor and birth, with the algorithm safely reducing exogenous insulin delivery (by ~50% of the total daily insulin dose) immediately after birth (36).

In our second randomized crossover home study we examined day and night HCL use for 28 days in 16 participants

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with a mean baseline HbA_{1c} of 8.0% (37). The TIRp was comparable, 60% during HCL and CGM with insulin pump therapy, but participants experienced less hypoglycemia during HCL use. Most participants (80%) reported less fear of hypoglycemia, but many expressed ongoing fear and worry about nocturnal events. All participants chose to continue HCL use, with median TIRp of 70% after 28 weeks' gestation (37). Likewise, most continued using HCL in hospital settings during and after birth, and 12 participants (75%) continued for up to 6 weeks postpartum. Postpartum CGM use was lower (16.5 h per day), but despite the use of prototype study devices (older CGM technology, algorithm housed on a tablet device) and demands of caring for a newborn, participants maintained 77% time in range 70–180 mg/dL for 6 weeks after birth (37).

These early-phase studies were of short duration with small numbers of participants and included use of earlier-generation HCL systems and control algorithms (19,35–37). CGM technology has improved with sensors that are licensed for use in pregnancy and accurate enough to be used for premeal insulin dosing (14). The HCL algorithm (CamAPS FX) was modified to allow customized glucose targets and more flexible user input, applicable for the gestational challenges of pregnancy. However, there were no adequately powered randomized trials evaluating the impact of HCL use on maternal glycemia when used throughout pregnancy among generalizable patient populations. We designed the AiDAPT trial to examine the clinical efficacy of using contemporary HCL therapy during T1D pregnancy, and to also explore women's and health care professionals' experiences (38).

AiDAPT

In AiDAPT, 124 pregnant women were randomized to closed loop (61) and standard care (CGM with usual insulin therapy) (63). At baseline, almost all participants (97%) were using CGM and approximately half were using insulin pump therapy (39). A training session (in-person or virtual) was conducted to provide support and education on personal glucose targets and specific features to intensify ("Boost") or reduce ("Ease-off") insulin delivery. Personal glucose targets were at users' and clinicians' discretion, but our recommended targets were 99 mg/dL in early pregnancy and 90 mg/dL from 16–20 weeks' gestation onward. Both study groups had the same CGM training and support and were advised to administer premeal insulin doses at least 15–30 min before eating. Both groups used their assigned CGM (Dexcom G6) or HCL (CamAPS FX) for >95% of the time during pregnancy (39). The mean personal glucose targets used by AiDAPT participants assigned to HCL were 102 mg/dL, 97 mg/dL, and 92 mg/dL in the first, second, and third trimesters, respectively.

We found significantly improved maternal glucose levels, with 10.5% higher TIRp (63–140 mg/dL) from 16 weeks' gestation until delivery in HCL participants in comparison with those assigned to CGM and their usual insulin delivery method (39) (Fig. 1). The TIRp benefits were achieved through reduction of maternal hyperglycemia across mildly-to-moderately severe thresholds, with less time spent >120, 140, and 180 mg/dL. There were notable improvements during the overnight hours (2300–0700 h), including 12.3% higher TIRp, less time with glucose <63 mg/dL, and fewer nocturnal hypoglycemic events. These improvements were remarkably consistent across baseline maternal HbA_{1c} categories, clinical sites, and pretrial insulin delivery (pump or multiple daily injections) (39). Mothers assigned to closed loop had 3.7 kg (8 lb) less gestational weight gain, most likely attributed to better matching of insulin to their daily food intake and fewer hypoglycemia treatments. A clinically relevant 5% higher TIRp was already apparent by the end of the first trimester, suggesting that the glycemic control benefits occurred very soon after commencement of HCL therapy. This is crucially important information for women and clinicians concerned about making therapeutic changes during early pregnancy. Furthermore, beyond the initial device training, HCL did not require additional health care team input; more clinic visits and more unscheduled contacts were observed for standard care participants. HCL participants had increased percentage of time with near-target glucose

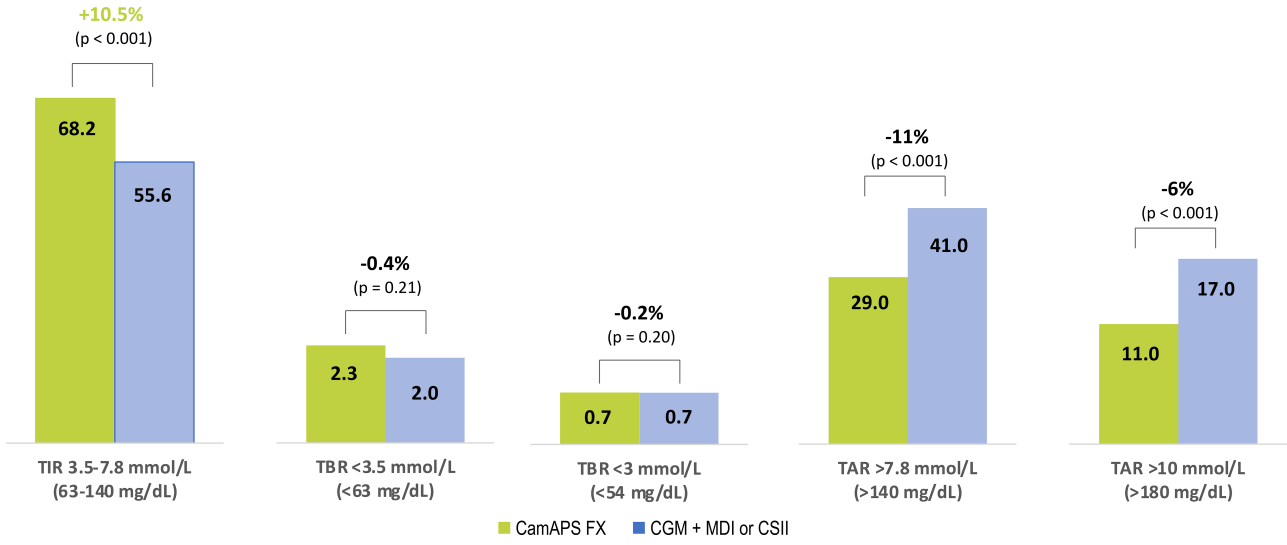

Figure 1—Glycemia among AiDAPT participants using closed loop compared with CGM with standard insulin delivery. Data are shown as percent time in range (TIR), time above range (TAR), and time below range (TBR). CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections. *P* values refer to the adjusted between-group treatment difference in linear mixed-effects regression models with adjustment for baseline CGM metric, insulin delivery method, and clinical site. Details of the statistical analyses have previously been published (39).

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levels (63–180 mg/dL), from 71% to 87%. To the best of our knowledge, this is the tightest glycemic control yet achieved through use of HCL, offering glycemic excursions that are less Alpine and more akin to Norbert Freinkel's "gentle foothills of the Berkshires."

HCL was used effectively throughout pregnancy across a remarkably representative patient population (Table 1), and without safety problems, including among those new to insulin pump therapy. Data regarding the in-hospital use of HCL therapy, including during the hospital admission for labor, birth, and the postpartum period, are currently being examined.

Babies of mothers in the HCL group were delivered 4.5 days earlier, without differences in birth weight, rates of preterm births, neonatal complications, or neonatal care unit admissions. There were four serious hypoxic ischemic birth injuries (one resulted in neonatal death) in the standard care group and one shoulder dystocia in the HCL group. The HCL group had notably lower rates of large-for-gestational-age birth weight babies in comparison with a national cohort (Table 2). Larger samples are needed to provide more definitive data on pregnancy outcomes and will require collaboration with other investigators (40).

Table 1—Representativeness of AiDAPT trial participants compared with a national population-based cohort of T1D pregnancies during 2019–2020

	AiDAPT, *N* = 124	NPID Audit, *N* = 4,175
Age[a]	31.1 ± 5.3	30 (22–37)
Duration of T1D[b]	17 ± 8	14 (3–25)
Non-White race/ethnicity (%)	7.0	9.3
Weight[c]	74.7 ± 15.2	70.0 (56.0–94.0)
BMI	27.4 ± 5.3	26.0 (21.2–34.0)
HbA_{1c} (%)[d]	7.7 ± 1.2	7.6% (6.2–10.2)
Folic acid use (%)	42.0	44.1
Smoking (%)	19.3	N/A
Diabetic retinopathy (%)	55.6	37.1
Multiple daily injections (%)	51.6	76.8
Miscarriage/termination (%)	33.0	N/A

Unless otherwise indicated data for AiDAPT participants are mean (SD) and those for NPID Audit are median (interquartile range). AiDAPT data have previously been published (39), and NPID Audit data are available from https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2019-and-2020. [a]Age range of AiDAPT participants was 19.7–44.7 years. Decimal point data not available for NPID Audit. [b]T1D duration of AiDAPT participants was 2–31 years. Decimal point data not available for AiDAPT or NPID Audit. [c]Maternal weight range of AiDAPT participants was 49.0–138.0 kg, with BMI 18.0–48.9 kg/m^2. [d]Entry HbA_{1c} of AiDAPT participants was 6.0%–14.0%. N/A, data not available.

WOMEN'S EXPERIENCES OF USING CLOSED LOOP

Pregnant women are acutely aware of the risks that antenatal hyperglycemia poses to their babies and highly motivated to optimize their glucose levels. However, in the light of their additional physiological challenges (nausea, hyperemesis, increased severe hypoglycemia risk, gestational delays in glucose disposal and insulin absorption), more stringent glucose targets, and intensively medicalized pregnancies, many experience psychological distress. Participants in AIDAPT described the intense, and sometimes relentless, physical, mental, and emotional demands of glycemic management: "constantly at the forefront of my mind," "every reading you see, you think, 'oh my God, I'm harming the baby.' So I was getting a lot of peaks and troughs, and I was finding that very stressful." Participants also contrasted their experiences with previous pregnancies with only finger-stick monitoring: "I didn't have a sensor, so I couldn't look back on what my sugars were doing through the night. So it was literally guessing" (41).

Women did not underestimate the challenges of starting HCL during early pregnancy, and many emphasized the importance of close oversight and additional emotional support in the first weeks of use. Despite rapid glycemic gains, usually within the first week of starting closed loop, women described taking several weeks adjusting to using the system before gradually building up their trust and confidence: "It felt as though I was just constantly watching, making sure that it was doing its job, so I would be probably looking at it anywhere between- I would probably say six to ten times a day." Most recognized the need to remain vigilant and engaged with daily self-management of T1D, a three-party collaboration between themselves, the HCL technology, and their health care teams: "I was like: normally I'd give a correction here, I'm going to put the Boost function on: is that

Table 2—Obstetric outcomes of AiDAPT closed-loop participants in comparison with a national population-based cohort of women with pregnancies with T1D

	Closed-loop users, *N* = 59	NPID Audit, *N* = 4,175
Gestational age (weeks)	36^{+3} ± 2	37 (34–38)
Preterm birth, <37 weeks (%)	45.7	42.5
Large for gestational age (%)	38.9	57.0
Small for gestational age (%)	5.1	5.4
Neonatal care admission (%)	22.0	51.0
Length of neonatal hospital stay (days)	6 (3–10)	6 (3–12)

Data for AiDAPT participants are mean ± SD and data for NPID Audit are median (interquartile range). AiDAPT data have previously been published (39), and NPID Audit data are available from https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2019-and-2020. There was one case of shoulder dystocia (2%) and there were five cases of respiratory distress (8%) in the AiDAPT closed-loop group, with frequent hyperbilirubinemia (68%), and/or neonatal hypoglycemia (44%), managed with oral or intravenous dextrose. Decimal point data are not available for gestational age at birth or neonatal length of hospital stay.

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right? . . . I used Ease-off a lot at work, especially if I could see that my blood glucose was sitting just slightly lower and I knew that maybe I wasn't having lunch for like another two hours or something, to then just try and prevent a hypo." Although the number of clinic visits and unscheduled antenatal contacts were fewer in HCL participants, participants reported receiving better and more timely health care team input (42,43): "So just because they've got all that data, they can then tell me the exact thing that I need to do. It allows me to communicate better, for them to understand better what I'm trying to say."

Importantly, women described substantial, quality of life benefits: "I have had to eat less to maintain my diabetes levels and eat what I want, when I want. This has meant I gained less weight and was able to stay more active which helped in so many other ways. I felt more trust in my own body for the first time in ages and confidence that I was doing my absolute best for my baby." Some noted that using HCL allowed them to remain longer in paid employment, which is crucially important for overcoming socioeconomic barriers in access to diabetes technology: "Honestly, it allowed me to work. I would never be able . . . to work at the job that I was doing [waitressing] at all, if I didn't have the machine." "I would have stopped work a lot more sooner than what I did . . . especially when you're self-employed, it does make a helluva lot of difference" (41).

HCL use allowed women to achieve the hitherto elusive pregnancy glucose targets, from 16 weeks' gestation until delivery, with clinical and quality of life benefits above and beyond what can be achieved by CGM alone (39). These results support NICE guideline recommendations that HCL therapy should be offered to women with T1D before and after pregnancy. Norbert Freinkel acknowledged the need for more aggressive therapy with exogenous insulin, and now we have the tools to translate this ambition into clinical reality. Finally, I wish to acknowledge that women's voices are often unheard or women are desexed as people, with potentially serious consequences, in relation to maternity care provision (44). These technological advances spanning 20 years of diabetes research would not have been possible without the active engagement, close collaboration, and continued support of women with lived experience of T1D pregnancy.

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