



Technological advances in pregnancy complicated by type 1 diabetes

Type 1 diabetes (T1D) in pregnancy is associated with considerably increased rates of adverse obstetric and neonatal outcomes. Nationwide studies confirm a two- to five-fold increased risk of congenital malformation, stillbirth and neonatal death.^{1–3} At least 50% of pregnancies are complicated by additional obstetric and perinatal complications, including pre-eclampsia, preterm delivery, delivery by caesarean section and large for gestational age (LGA) offspring, with data suggesting that rates of LGA and fetal macrosomia are increasing.^{3,4} The importance of avoiding hyperglycaemia to reduce obstetric complications, neonatal morbidity and LGA is well recognised.^{5,6} Therefore, to deliver healthy infants, women with T1D are advised to carefully plan their pregnancies, attend structured education/prepregnancy care (PPC) and aim for near-normal blood glucose levels before and during pregnancy.⁷ However, many pregnancies are unplanned and even the most motivated women attending structured education and PPC struggle to achieve optimal glycaemic control.^{4,8} During 2006–2009, only 10% of women with T1D who attended PPC in East Anglia achieved preconception HbA_{1c} levels <6.1% (43mmol/mol). Consequently, despite improved preconception counselling and increased PPC attendance, glycaemic control and pregnancy outcomes remained suboptimal. Technological advances were not routinely available, 90% of women used multiple daily injections (MDI) without continuous glucose monitoring (CGM), and only 10% of women had continuous subcutaneous insulin infusion (CSII) therapy before or during pregnancy. Audit data confirm similarly poor glycaemic control and pregnancy outcomes across the UK.⁹

Technological advances in type 1 diabetes outside pregnancy

Outside pregnancy, there have been unprecedented advances in the technology available for managing T1D, with growing acknowledgement of the potential benefits of CGM, CSII and, most recently, sensor augmented pump (SAP) therapy. Several studies confirm the benefits of regular real-time or personal CGM use (>6 days per week) in achieving tight glycaemic control among children and motivated adults.^{10–12} However, these studies also highlight the challenges in adolescents (presumed to be less motivated) and limitations of CGM in preventing hypoglycaemia, with frequent and prolonged nocturnal episodes despite regular CGM use.¹³ A recent health technology assessment concluded that pump therapy offers advantages over MDI: namely, better blood glucose control, improved quality of life and reductions in hypoglycaemic episodes, blood glucose swings, dawn phenomenon and total daily insulin dose (TDD) both in paediatric and in adult populations.¹⁴ Sensor augmented pump (SAP) therapy integrating CGM with CSII also demonstrates improved

glycaemic control (average HbA_{1c} reduction of 0.6% compared to MDI) without increased hypoglycaemia (severe hypoglycaemia or sensor observed biochemical episodes) in children and adults, suggesting that CGM may be more successful when combined with CSII.¹⁵

During the past five years, the Juvenile Diabetes Research Foundation (JDRF) has accelerated the momentum towards closed-loop insulin delivery, marking a new era in diabetes management whereby computerised mathematical algorithms are used to link insulin delivery with real-time CGM glucose levels. Since then, studies from Cambridge have focused on overnight closed-loop insulin delivery, demonstrating approximately 20% increased time in target and reduced nocturnal hypoglycaemia, using a model predictive control (MPC) algorithm, both in children and in adults.^{16,17} Others have explored the safety and efficacy of different control algorithms, intraperitoneal insulin delivery and bi-hormonal systems.^{18–21} Most conclude that improving insulin dosing around meals and exercise will be required to move from overnight to 24-hour closed-loop, with faster acting insulin analogues needed for optimal postprandial glucose control.

Evidence base for technology in pregnancy

Unfortunately, the evidence base for new technologies in pregnancy remains limited. Using retrospective or professional CGM, we have shown that even highly motivated T1D pregnant women (73% attended PPC, mean HbA_{1c} 5.9% [41mmol/mol]) using MDI spent on average eight hours per day hyperglycaemic (sensor glucose >7.8mmol/L) and two hours per day hypoglycaemic (sensor glucose <3.5mmol/L) during the second and third trimesters.²² We also demonstrated that integrating professional CGM into routine antenatal care was associated with an average HbA_{1c} reduction of 0.6% in late gestation and reduced the risk of LGA.²³ While women wore a blinded, seven-day CGM approximately four times throughout pregnancy, their sensor data were used in a standardised patient-centred fashion as an educational tool to make dietary, lifestyle and/or insulin dose adjustments. There are as yet no published randomised studies of personal (real-time) CGM in pregnancy, although a Danish study is nearing completion and an international JDRF funded study ('Continuous glucose monitoring in women with type 1 diabetes during pregnancy trial – CONCEPTT') will commence this year.

The use of CSII in pregnancy is well established and supported by the recent NICE guidelines.⁷ Advocates (including these authors) believe that the benefits demonstrated in patients with T1D outside pregnancy are likely applicable before and during pregnancy. However, there is a lack of randomised controlled trials, with systematic reviews in pregnancy finding no advantages or disadvantages of CSII over MDI.^{14,24,25}



Case-control studies confirm that women using CSII are more likely to attend PPC, and therefore achieve lower HbA_{1c} levels during early pregnancy.^{26,27} There are no adequately powered studies to evaluate the impact of CSII on glycaemic control during late pregnancy or on perinatal outcomes. It is unclear whether women with poor glycaemic control during the first trimester would benefit most from CGM, CSII or SAP during pregnancy.

The Closed Loop in Pregnancy (CLIP) project

Our group has begun to refine, develop and evaluate overnight and prandial algorithms for pregnant women with T1D. The vital component of a closed-loop system for use during pregnancy is a computer algorithm which can function safely despite the physiological challenges of pregnancy – namely, changes in gastric emptying, gluconeogenesis and insulin kinetics.²⁸ As the glycaemic control targets are tighter during pregnancy, our first steps have been to document CGM sensor accuracy and to evaluate the safety and efficacy of overnight closed-loop insulin delivery, in early (12–16 weeks) and in late (28–32 weeks) gestation. We are also using stable label isotopes to document the meal-related glucose fluxes and endogenous glucose production during T1D pregnancy.

Our pilot feasibility study (CLIP-01) studied 10 T1D pregnant women (five on MDI, five on CSII) with varying levels of glycaemic control (HbA_{1c} 5.7–8.7% [39–72mmol/mol]), diabetes duration (2–26 years) and insulin sensitivities (TDD 0.3–1.0 units/kg/day) over two 24-hour periods (12pm–12pm) during early and late pregnancy. A single CGM sensor (FreeStyle Navigator, Abbott Diabetes Care) was calibrated as per the manufacturer's instructions and inserted the day before each study visit. All women were connected to an insulin pump (Deltec Cozmo, Smiths Medical) delivering rapid acting insulin analogue aspart. At 6pm, they ate a standardised dinner (80g carbohydrate: pasta with vegetables and tomato sauce) followed by an overnight fast and a rapid acting high carbohydrate breakfast (60g carbohydrate: orange juice and toast with jam) at 7am the following morning. Prandial insulin doses were calculated by women using capillary glucose levels and their usual insulin to carbohydrate ratios. Basal insulin infusion rates were advised by the MPC algorithm and manually adjusted by a research nurse every 15 minutes. The algorithm was initiated with three CGM measurements, maternal weight and total daily insulin dose. Our results confirmed that sensor accuracy is comparable to that outside pregnancy; 94.6% of CGM glucose values were within the clinically acceptable target range (Clarke error zones A and B) with median absolute relative differences between paired sensor and plasma glucose levels of 11.4%. During the overnight period (11pm–7am), women spent on average 84% of time with plasma glucose levels within the recommended target range (3.5–7.8mmol/L) in early pregnancy and 100% of time in target during late pregnancy.²⁹

This provides the first observational data on closed-loop insulin delivery during pregnancy, suggesting that the MPC algorithm coped well with intra-individual and gestational variability to adjust insulin delivery safely during early and late gestation. It highlighted the

challenge of matching prandial insulin doses to carbohydrate rich meals, with only 47–59% of time in target after breakfast and 68–77% of time in target after dinner. We anticipate that further analyses of the carbohydrate metabolism and insulin absorption kinetics may assist prandial insulin dosing during pregnancy. Our next steps are to perform randomised controlled trials of closed-loop insulin delivery, with our subsequent study protocol (CLIP-02) incorporating two 50-minute sessions of moderate physical activity (ranging from 2.0 to 3.5 METs [metabolic equivalents]). If nocturnal near-normoglycaemia can be maintained following exercise, then progression to overnight studies in the home setting would be warranted.

Technological innovations enhance many aspects of modern life (iPods, smartphones) and could mark a new era in improving the day to day life of people with T1D. While pregnant women may benefit most from recent technological advances, they have been a relatively marginalised study population. To improve health outcomes for women and their offspring with T1D, new technologies including CGM, CSII, SAP and closed-loop algorithms must be informed by scientifically rigorous data of their safety and efficacy during pregnancy, just as they are outside pregnancy.

Dr Helen R Murphy, MD¹

Dr Daniela Elleri, MD^{1,2}

Dr Kavita Kumareswaran, MBCh¹

Dr Roman Hovorka, PhD^{1,2}

¹Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, UK

²Department of Paediatrics, University of Cambridge, UK

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Declaration of interest

HRM: speaker's honoraria from Minimed Medtronic. RH: speaker's honoraria from Minimed Medtronic, Lifescan, Novo Nordisk; serves on Animas advisory panel. RH: licence fees from Becton Dickinson, and patent applications.

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