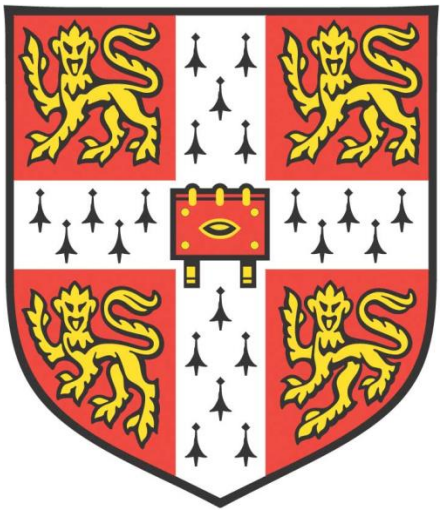
Glycaemic control in pregnancies complicated by type 1 diabetes



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This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed the prescribed word limit for the Degree Committee of Clinical Medicine.

Statement of contributions

The closed-loop studies presented in Chapters 2, 3, 4, and 5 were conceived and designed by Prof Helen Murphy, Dr Roman Hovorka, and Dr Zoë Stewart. Regulatory approvals were obtained by Prof Helen Murphy and Dr Zoë Stewart. Participants were recruited by Dr Zoë Stewart, Prof Helen Murphy, and Sara Hartnell. Participants were trained by Dr Zoë Stewart and Sara Hartnell, who also provided troubleshooting and advice for the participants. Study visits were conducted by Dr Zoë Stewart, Sara Hartnell, and Prof Helen Murphy. Participant interviews were conducted by Dr Conor Farrington. Data management was done by Dr Zoë Stewart with assistance from Jenni Curtis during the day-and-night study. Data analysis and results interpretation was performed by Dr Zoë Stewart. Qualitative data were analysed and interpreted by Dr Zoë Stewart, Dr Conor Farrington, and Prof Helen Murphy. Sleep data were analysed by Dr Zoë Stewart and Dr Eleanor Scott. Questionnaire data were analysed by Dr Zoë Stewart and Prof Katherine Barnard. Labour and delivery data were analysed and interpreted by Dr Zoë Stewart with assistance from Dr Jennifer Yamamoto.

The study of continuous glucose monitoring in mother-infant pairs was designed by Prof Helen Murphy, Dr Kathryn Beardsall, and Dr Zoë Stewart. Participants were recruited by Dr Zoë Stewart and Prof Helen Murphy. Maternal CGM sensors were inserted by Dr Zoë Stewart. Infant CGM sensors were inserted by Dr Zoë Stewart and Lynn Thomson. Data were downloaded, analysed, and interpreted by Dr Zoë Stewart under the supervision of Prof Helen Murphy and Dr Kathryn Beardsall.

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Abstract

Type 1 diabetes in pregnancy is associated with higher rates of maternal and infant complications. The complications are associated with maternal hyperglycaemia. Thus, the main goal of treatment for these women is to optimise glycaemic control and thereby improve clinical outcomes for themselves and for their baby.

This thesis examines glycaemic control in the mothers and infants of pregnancies affected by type 1 diabetes. I present the first home studies of closed-loop insulin delivery in this population. The aim of these studies was to assess the feasibility, efficacy, and utility of overnight and then day-and-night closed-loop insulin delivery in pregnant women with type 1 diabetes. The overnight study, which examined 16 pregnant women (mean age 34.1 years, HbA1c 6.8%, 14.4 weeks gestation), compared overnight use of the closed-loop system with sensor-augmented pump therapy in a 2x4-week randomised crossover design. We found that closed-loop therapy was associated with a 15% improvement in overnight time spent with target glucose concentration (3.5-7.8 mmol/L; 74.7% during closed-loop use vs 59.5% during sensor-augmented pump therapy use). The day-and night study also examined 16 pregnant women (mean age 32.8 years, HbA1c 8.0%, 16.4 weeks' gestation) using a 2x4-week randomised crossover design to compare continuous day-and-night use of closed-loop insulin delivery with sensor-augmented pump therapy. This study enrolled a more diverse range of participants than the overnight study, but found that closed-loop therapy was associated with comparable glucose control and significantly less hypoglycaemia than sensor-augmented pump therapy. Chapter 4 examines women's experiences of using the closed-loop system during pregnancy. While the system was generally well-received by participants, individual interactions and perceptions of the system varied markedly, and often did not align with biomedical measures of glycaemic response.

After participation in either crossover study, participants could choose to continue using the technology until delivery (overnight study), or until 6 weeks post-partum (day and night study). Those data are presented in Chapters 2 and 3. The combined data from the women who used the closed-loop system during labour and delivery in either study are presented in Chapter 5. Tight glycaemic control during labour and delivery has traditionally been considered important for reducing rates of neonatal hypoglycaemia.

However, despite very tight maternal glycaemic control in the women who used closed-loop insulin delivery, rates of neonatal hypoglycaemia were high.

In order to better characterise the relationship between maternal glucose control in type 1 diabetes pregnancy and neonatal hypoglycaemia, Chapter 6 details an observational study in which continuous glucose monitoring was used to measure maternal and neonatal glycaemic control in 16 mother-infant pairs. The study found that, while neonatal hypoglycaemia was very frequent, it was generally, but not always, detected and treated effectively.

Together, these studies suggest that a novel management tool, closed-loop insulin delivery, can improve overnight glycaemic control, and perhaps reduce hypoglycaemia during type 1 diabetes-affected pregnancies above what is possible with currently available treatments. However, complication rates remain high for these women and their babies. Further research is needed both to further develop treatments that can improve maternal glycaemic control, and to better understand the pathogenesis of diabetes-related pregnancy complications, with the ultimate goal of improving outcomes for women and their children. A definitive trial to assess the clinical efficacy, patient acceptability, and cost effectiveness of closed-loop is now warranted.

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List of abbreviations

ADA	American Diabetes Association
ANOVA	Analysis of variance
AUC	Area under the curve
CGM	Continuous glucose monitoring
CL	Closed-loop insulin delivery
CSII	Continuous subcutaneous insulin infusion
DCCT	The Diabetes Control and Complications Trial
DTQ	Diabetes Technology Questionnaire
HbA1c	Glycated haemoglobin
HELLP	Haemolysis, Elevated Liver enzymes, Low Platelet count
HFS II	Hypoglycaemia Fear Survey II
IUGR	Intrauterine growth restriction
IV	Intravenous
IVF	In vitro fertilisation
LBGI	Low blood glucose index
MAGE	Mean amplitude of glucose excursion
MDI	Multiple daily injections of insulin
MPC	Model predictive control
NICE	The National Institute for Health and Care Excellence
PID	Proportional integral derivative
SAP	Sensor-augmented pump therapy
SD	Standard deviation
SMBG	Self-monitored blood glucose
TOP	Termination of pregnancy
UK	United Kingdom
VRII	Variable rate insulin infusion
WHO	World Health Organization

1. Introduction

The maternal and infant complications of diabetes in pregnancy are widely recognised and include higher rates of congenital anomaly, stillbirth, neonatal death, and macrosomia (1). These complications can be partially mitigated with good glycaemic control (2–5).

However, women with type 1 diabetes face a number of challenges when it comes to achieving and maintaining tight glycaemic control during pregnancy. Hormonal and other factors cause insulin requirements to change with advancing gestation and to be difficult to accurately predict (6,7). Even with regular glucose monitoring, intensive insulin therapy and "safe" HbA1c levels, women with type 1 diabetes spend an average of 12 hours daily with their glucose concentration outside the recommended range (8). Further, women with type 1 diabetes are at particular risk of hypoglycaemia during pregnancy (6,9–11), so the benefits of tight glycaemic control must be weighed against the increased risk of hypoglycaemia.

Advances in technology for both glucose monitoring and insulin delivery such as continuous glucose monitoring (CGM), insulin pumps, and sensor-augmented pump therapy (SAP) offer the potential of improved glycaemic control; however, their

effectiveness in pregnancy and impact on obstetric and neonatal outcomes need further evaluation (12).

Closed-loop systems use glucose measurements obtained via CGM and a control algorithm to adjust insulin delivery in real time. Initial data suggest that closed-loop systems may be able to maintain excellent glycaemic control and prevent nocturnal hypoglycaemia in pregnant women with diabetes (13,14).

1.1 Diabetes

1.1.1 Definition

Diabetes mellitus is a chronic condition in which insulin insufficiency or ineffectiveness results in hyperglycaemia (15). It is associated with microvascular complications (retinopathy, neuropathy, and nephropathy) and macrovascular complications (ischaemic heart disease, peripheral vascular disease, and stroke), reduced life expectancy, and reduced quality of life.

The World Health Organization (WHO) diagnostic criteria for diabetes are a fasting plasma glucose greater than or equal to 7.0 mmol/L, and/or a plasma glucose concentration greater than or equal to 11.1 mmol/L two hours after a glucose load (15).

1.1.2 Types

The three most common types of diabetes are type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes is characterised by autoimmune destruction of the pancreatic beta cells resulting in complete or near-complete insulinopenia (16). Type 2

diabetes, which accounts for 95% of all diabetes cases, is a condition of insulin resistance or insulin ineffectiveness leading first to hyperinsulinaemia, and eventually to a decline in beta cell function, and reduction in circulating insulin levels (17). Gestational diabetes is defined as any degree of hyperglycaemia first detected in pregnancy (18). The pathogenesis of gestational diabetes is thought to be similar to that of type 2 diabetes, and having had gestational diabetes significantly increases a woman's risk of developing type 2 diabetes later in life.

1.1.3 Prevalence

Globally, more than 422 million people live with diabetes, and the rates are rapidly rising (19). The prevalence of diabetes in people over 18 years of age is more than 8.5% (19). In the UK, 3.5 million people are currently diagnosed with diabetes and more than half a million more are estimated to have the disease but have not yet been diagnosed. This represents approximately 6% of the UK population. In the UK, approximately 90% of people with diabetes have type 2 diabetes, and 10% have type 1 diabetes or other rarer forms of the condition (20). Globally, two in five women who have diabetes are of reproductive age (21).

1.2 Type 1 diabetes and pregnancy

1.2.1 Prevalence

Diabetes is the most common medical condition affecting pregnancy, and affects approximately five percent of pregnancies in the UK (22). Gestational diabetes accounts for approximately 87.5% of diabetes in pregnancy cases. In the UK, over 1600 women with pre-existing type 1 diabetes have pregnancies each year (23).

1.2.2 Complications

In people with type 1 diabetes, exposure to hyperglycaemia increases risk of short and long term health complications (24). In the short term, hypoglycaemia secondary to insulin therapy can lead to altered conscious state, coma, and death (25). Significant hyperglycaemia can lead to diabetic ketoacidosis and be life-threatening (26).

In the longer-term, hyperglycaemia increases the risk of microvascular complications including retinopathy, nephropathy, and autonomic and peripheral neuropathy, as well as macrovascular complications including ischaemic heart disease, stroke, and peripheral vascular disease (24,27,28).

People with diabetes also experience higher rates of depression, lower quality of life, and shorter life-expectancy than their counterparts without diabetes (29–32).

Pregnancy can increase the risk of diabetes complications, and obstetric and neonatal complications are common in women with type 1 diabetes in pregnancy.

1.2.2.1 Maternal complications

Women with type 1 diabetes in pregnancy face a range of complications. In weeks 10 to 20 of pregnancy, insulin sensitivity is high and women are particularly prone to hypoglycaemia (6,33–35). Further, some women experience diminished or altered symptoms of hypoglycaemia during pregnancy. Together this change in hypoglycaemia awareness and increased propensity of hypoglycaemia render women at particularly high risk of severe hypoglycaemic episodes and even maternal death from hypoglycaemia during pregnancy. In the UK, almost one in 10 women with type 1 diabetes have hypoglycaemia requiring hospital admission during their pregnancy (36).

During pregnancy, women with type 1 diabetes also develop ketones at relatively lower glycaemic levels and more quickly than those who are not pregnant. This places them at higher risk of developing diabetic ketoacidosis (37). Additionally, symptoms of diabetic ketoacidosis can be difficult to distinguish from pregnancy-related nausea and vomiting, which can also lead to reduced carbohydrate intake and subsequent formation of ketones.

There is some evidence that diabetes-related retinopathy can progress more rapidly during pregnancy (38–40) especially among women with previous retinopathy and poor control in early pregnancy. It appears that pregnancy complications are more common in women with nephropathy (41), pregnancy does not alter survival rates in women who have diabetic nephropathy (42,43). In women without nephropathy, pregnancy is not associated with worsening renal function (42,43) although some studies have suggested that women with an elevated creatinine level are more likely to have progression of their nephropathy during pregnancy (44–46).

1.2.2.2 Obstetric complications

Women with type 1 diabetes in pregnancy experience higher rates of a range of obstetric complications. Approximately 15% of pregnant women with type 1 diabetes develop pre-eclampsia, representing a 5-6 fold increase in risk compared with pregnant women without diabetes (47–50). Women with higher glycated haemoglobin levels face increased odds of developing pre-eclampsia (50). Pre-eclampsia places women at higher risk of fetal intrauterine growth restriction (IUGR), pre-term delivery, caesarean section and stillbirth, and is associated with complications including pulmonary oedema, eclampsia, HELLP (Haemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome, stroke, and maternal death.

Approximately 65% of women with type 1 diabetes in pregnancy deliver via caesarean section in the UK (36). About half of these are booked as elective procedures with the remainder occurring in an emergency setting. The reasons for caesarean section vary

widely, but higher rates of overweight and obesity, pre-eclampsia, induction of labour and pre-term delivery are significant contributors. Additionally, the higher risk of stillbirth may lower the threshold for intervention in cases of reduced fetal movements or abnormal fetal cardiotocography.

Shoulder dystocia is a complication of vaginal delivery in which specific obstetric manoeuvres are required because simple traction has failed to deliver the fetal body after the delivery of the head (51). Shoulder dystocia is an obstetric emergency and is associated with maternal, and particularly fetal, morbidity and mortality. It is associated with perineal trauma, post-partum haemorrhage, fetal brachial plexus injury and clavicular fracture, and stillbirth (52). Risk factors for shoulder dystocia include fetal macrosomia, raised maternal BMI, induction of labour, and maternal diabetes. Infants of women with diabetes are between two and four times more likely to experience shoulder dystocia than infants of the same birthweight born to women without diabetes (53,54).

1.2.2.3 Infant complications

Infants of women with type 1 diabetes in pregnancy experience higher rates of both short- and long-term complications. These infants have a two-to-three fold increased risk of major congenital anomaly. This increased rate of anomaly is thought to be a result of exposure primarily to hyperglycaemia, but also potentially to hypoglycaemia and other metabolites (e.g., ketones) in the peri-conception and early gestational period. Neural tube defects are particularly associated with hyperglycaemia and are found in one percent of infants of women with diabetes in pregnancy. (1,41,55–58)

Stillbirth is two to five times more common in pregnancies affected by pre-existing diabetes (1,23,36,59,60). Although the majority of stillbirths in women with diabetes occur prior to 36 weeks gestation (58,61), the excess diabetes-related risk of stillbirth is evident from 32 to >39 weeks' gestation (62). UK guidelines advise women with type 1

diabetes to have an induction of labour at 38+6 weeks gestation to reduce the risk of late stillbirth (22).

Infants of women with type 1 diabetes are delivered preterm 22-42% of the time, representing a four-to-eight-fold relative risk of preterm birth compared to singleton infants of women without diabetes (47,63,64). Pre-term delivery can occur as a result of spontaneous labour or medical intervention (either induction of labour or caesarean section) that is indicated for maternal or fetal risk reduction. Among women with type 1 diabetes, pre-term delivery is more common for those who are nulliparous, have pre-eclampsia, experience progression of nephropathy in pregnancy, and have HbA1c levels above 7% (65).

Approximately 50-60% of infants born to women with type 1 diabetes are large-for-gestational-age (>90th centile) (36,47). Large-for-gestational-age infants are more common in women with poorer glycaemic control (66). Maternal hyperglycaemia results in transfer of glucose to the fetus and subsequent fetal hyperinsulinaemia (67). This fetal hyperinsulinaemia results in excess fetal growth and frequent neonatal hypoglycaemia as the maternal glucose source is no longer present after delivery. Approximately two in three infants of women with type 1 diabetes have neonatal hypoglycaemia (47,68,69), which, if left untreated, can result in neurodevelopmental impairment (70). However, it is now commonplace to screen such infants for neonatal hypoglycaemia, and infants requiring treatment receive additional oral or nasogastric feeds, or intravenous dextrose treatment as appropriate.

The combined effects of these neonatal complications result in infants of women with type 1 diabetes being admitted to neonatal intensive care units more frequently than those unexposed to diabetes (47). Admission rates vary considerably across different regions and services (36).

While our understanding of the life-long impact of intrauterine exposure to maternal type 1 diabetes remains incomplete, there is increasing evidence to suggest higher rates of metabolic disease, obesity, and type 2 diabetes in offspring of women with type 1 diabetes.

1.2.3 Pregnancy-related changes in physiology

Physiological changes in pregnancy pose particular challenges for women with diabetes and their clinicians. Not only are the blood glucose targets tighter than for non-pregnant people, but the changes in carbohydrate metabolism, insulin resistance and insulin pharmacokinetics are difficult to predict precisely, making it especially difficult to achieve and maintain optimal glycaemic control.

In early pregnancy, women with diabetes often experience a period of glycaemic instability, which has been attributed to high levels of chorionic gonadotropin, progesterone, and thyroid hormones (6). This is generally followed by a period of increased insulin sensitivity between approximately weeks 10 and 16-20 (6,33,34). In women with type 1 diabetes, this results in an increased propensity for hypoglyaemia and often requires a reduction in insulin dose.

As pregnancy progresses, women develop increasing insulin resistance and generally require relatively rapid insulin dose escalation throughout the second and much of the third trimesters of pregnancy (71–73). These changes are thought to be driven by increased tumour necrosis factor (74), placental growth hormone, and insulin-like growth factor-I (75,76).

While glucose absorption remains relatively stable throughout pregnancy, post-prandial glucose disposal via peripheral muscle glucose uptake slows with advancing gestation (77). This results in prolonged post-prandial glucose elevation. In addition, time to peak insulin activity is delayed with advancing gestation. In a study of 22 pregnant women with type 1 diabetes using the rapid acting insulin analogue insulin aspart, the time-to-peak aspart concentration increased by approximately 50% between 8 and 38 weeks gestation (78), representing a slower onset of action. The study also found marked within-patient variability in insulin pharmacokinetics, which is reflected in the clinical

challenges of day-to-day glycaemic management of type 1 diabetes in pregnancy. The concurrent changes in carbohydrate metabolism and insulin pharmacokinetics make it increasingly difficult to accurately match insulin dosing with carbohydrate intake and frequently result in periods of post-prandial hyperglycaemia (77).

In order to combat these changes in carbohydrate metabolism and insulin resistance, increased pre-prandial insulin doses are generally required as pregnancy progresses. Additionally, extending the interval between insulin administration and meal times can improve glycaemic control by better aligning insulin action time with the post-prandial glucose peak (77,78).

1.2.4 Measures of glycaemic control

Given the association between hyperglycaemia and diabetes-related complications, measuring glycaemic control is a crucial part of managing type 1 diabetes both in and outside of pregnancy. Mean glucose can be calculated on the glucometer from capillary blood glucose measurements, but the clinical utility of figures calculated this way are proportionate to the number of pre- and post-meal measurements taken.

The most common measure of assessing average glycaemic control outside of pregnancy is glycated haemoglobin (HbA1c). This measure is useful for evaluating population-level glucose control and quantifying the risk of complications, but has limitations when used for evaluating the glucose control of an individual. Although assay methodology has improved, inherent limitations of the test itself are apparent, most notably that patients with the same mean glucose can have different HbA1c values (79). The Diabetes Control and Complications Trial demonstrated that a mean plasma glucose of 10 mmol/litre could be associated with an HbA1c between 6% and 11% (80). In populations without diabetes, HbA1c is lower during pregnancy (81). The reduction is attributed to lower mean glucose concentrations and to gestational changes, including increased erythropoiesis, shortened red cell life span, reduced red cell affinity for glucose, and iron deficiency in pregnancy (82–88). Observational studies of pregnancies complicated by

diabetes also suggest a glycaemic-independent lowering of HbA1c (approximately 0.5% reduction) (85,89).

HbA1c is commonly used to assess glucose control and to quantify risk in pregnancies complicated by pre-existing diabetes (49,90,91). Higher HbA1c levels are associated with higher risk of diabetes-related pregnancy complications (3,66). As such, current NICE guidelines suggest measuring HbA1c levels at the booking appointment and to "consider measuring HbA1c levels in the second and third trimesters of pregnancy" to assess the level of risk for the pregnancy. However, they also advise that "HbA1c should not be used routinely for assessing glycaemic control in the second and third trimesters of pregnancy" (22). When HbA1c is used in pregnancy, it is important to recognise that its relationship with mean glucose is different from outside of pregnancy, and if an average glucose estimation is calculated, a pregnancy and trimester-specific formula should be used (92).

Serum fructosamine is also used as a measure of medium-term glycaemic control for people with diabetes. It has been proposed for use in pregnancy because it is unaffected by red cell turnover and lifespan, and by anaemia (93). Fructosamine also reflects a shorter time period than HbA1c, which might be particularly beneficial in pregnancy when insulin requirements and glucose control change more rapidly, requiring more frequent insulin dose adjustments. However, studies investigating the correlation between fructosamine and HbA1c or mean glucose in pregnancy have had inconsistent results (94–98). The reproducibility of fructosamine is poor and it has not been well correlated with pregnancy outcomes. Therefore, its utility in the management of diabetes in pregnancy remains unclear and it is not commonly used.

1.3 Management of type 1 diabetes in pregnancy

Management of type 1 diabetes in pregnancy is difficult. All efforts to optimise glycaemic control have to be balanced against the risk of maternal hypoglycaemia. Even with modern treatments and concerted research efforts over recent decades, there has been no substantial improvement in clinical outcomes for women with type 1 diabetes in pregnancy since the 1989 St Vincent Declaration (99) which set a target of achieving complication rates in women with diabetes that approximate those of the general obstetric population (1,100–102). Pregnancy-related physiological changes make it difficult to accurately predict insulin requirements and therefore to anticipate required changes in insulin doses for women with type 1 diabetes. Nonetheless, advances in our understanding of diabetes in pregnancy, faster-acting insulin analogues, and new diabetes technologies have contributed positively to the treatment of type 1 diabetes in pregnancy.

1.3.1 Current guidelines

Numerous national guidelines exist to provide specific guidance with regards to the management of diabetes in pregnancy. With regards to type 1 diabetes in pregnancy, The United Kingdom's National Institute for Health and Care Excellence (NICE) (22) and the Canadian Diabetes Association (103) recommend that women measure their capillary blood glucose concentration seven times per day and aim for a blood glucose below 5.3 mmol/L when fasting and below 7.8 mmol/L one hour after meals and are reviewed by their medical team every one to two weeks. Post-prandial glucose monitoring is particularly important in pregnancy and has been associated with a reduction complications for women with type 1 diabetes (104). NICE guidelines recommend the use of rapid-acting insulin analogues during pregnancy, which should be delivered via multiple daily injections (MDI), or an insulin pump if glucose control remains suboptimal without disabling hypoglycaemia using MDI therapy (22). They suggest that continuous glucose monitoring should be considered for pregnant women who have problematic severe hypoglycaemia or unstable blood glucose, or where further information is required about glucose variability.

The American Diabetes Association recommendations for the management of type 1 diabetes in pregnancy are similar (91): they suggest that women aim for a fasting blood glucose concentration ≤5.0 mmol/L and a one-hour post-prandial concentration of ≤7.2-7.8 mmol/L if these values can be safely achieved without significant hypoglycaemia. The ADA recommends the referral of all women with type 1 diabetes to a specialised centre, where they have access to a multi-disciplinary team including a high-risk obstetrician, endocrinologist, dietician, nurse, and social worker.

The ADA recommend measuring HbA1c each trimester, aiming for as close as possible to 6-6.5% without significant hypoglycaemia (22,91).

Danish recommendations also advise management in a specialised unit with a multi-disciplinary team and visits every one to two weeks (105). However, they suggest blood glucose targets of 4-6 mmol/L fasting, 4-5.5 mmol/L pre-meals, 4-7 mmol/L 1.5 hours post-meals, 6-8 mmol/L before bed, and 5-7 mmol/L overnight. With regards to HbA1c, they recommend aiming for <6.5% prior to 20 weeks' gestation and <5.6% after 20 weeks' gestation.

1.3.2 Insulin pumps

In non-pregnant cohorts, insulin pumps that deliver insulin continuously via a subcutaneous catheter have been demonstrated to achieve better glucose control with less frequent hypoglycaemia than conventional multiple daily injections of insulin (MDI) (106,107). However, the benefits of pump therapy are less clear in pregnancy. There have been relatively few trials comparing pump therapy with multiple daily injections during pregnancy, and most studies have been retrospective observational studies examining small numbers of patients. Further, the majority of extant data derive from older studies conducted with older generation devices without bolus calculators and at a time when clinicians were less familiar with the use of insulin pumps. They also predate

the development of rapid-acting insulin analogues such as aspart and lispro, which are used routinely in current clinical practice.

Extant literature suggests that the use of insulin pumps during pregnancy is safe and achieves similar metabolic and neonatal outcomes as conventional treatment (108–116), with some studies finding lower rates of small-for-gestational-age infants (117), fewer episodes of hypoglycaemia, (118) and lower insulin requirements (115,118–120) in women receiving insulin pump therapy.

A 2011 and subsequent 2016 Cochrane Collaboration review of prospective trials of CSII vs MDI in pregnancy found a paucity of randomised controlled trials. Meta-analysis of included trials demonstrated the possibility of a clinically insignificant increase in mean birthweight when CSII was used (although wide confidence intervals mean this finding is uncertain), but no difference in macrosomia, caesarean section rates, perinatal mortality, fetal anomaly, maternal hypoglycaemia, maternal hyperglycaemia or small-for-gestational-age infants (121,122). Another meta-analysis of six studies (107 women on CSII vs. 106 on MDI) showed comparable glucose control and pregnancy outcomes (114). These studies had very small sample sizes (mean 18 pregnancies per treatment arm) and lacked power to detect differences in maternal/infant outcomes.

However, some observational studies have suggested increased rates of severe maternal hypoglycaemia (115), ketoacidosis, neonatal hypoglycaemia (123), large-for-gestational-age infants and perinatal mortality (117) when insulin pump therapy is used in pregnancy. Given the highly selected patient populations and small sample sizes, the generalisability of these results are unclear.

The majority of insulin pump studies in pregnancy have been retrospective and observational in nature. Women who are commenced on insulin pump therapy often have a longer duration of diabetes and are more likely to already have microvascular

complications (108,113,119). Therefore, it may be that the increased rates of complications reflect a more severe glycaemic disturbance.

A retrospective analysis of 387 consecutive pregnancies of women with type 1 diabetes from three Canadian centres found lower HbA1c measurements in women treated with pump therapy compared to those treated with MDI and no difference in frequency of severe hypoglycaemia, diabetic ketoacidosis, or caesarean sections (124). In this study, women on pump therapy started with lower pre-pregnancy HbA1c values and were more likely to have had pre-conception care. Women treated with pump therapy were more likely to have large-for-gestational-age infants with a trend towards a higher frequency of neonatal hypoglycaemia but no difference in other neonatal outcomes.

Insulin pumps can offer easier titration of doses, which is particularly relevant in pregnancy when insulin requirements are highly variable (6,125), and increased user satisfaction and quality of life compared to multiple daily injections (116,126,127). Therefore, some benefit may be conferred by using insulin pumps even if glycaemic control and maternal-fetal outcomes remain unchanged (128).

Given advances in our understanding of physiology, the development of new insulin analogues, and improved practitioner familiarity with the use of pump therapy, many argue that published literature regarding the use of insulin pumps in pregnancy is outdated and that, if used correctly, CSII may confer benefits including improved glycaemic control, similar to what is seen in non-pregnant populations. Large adequately powered randomised controlled trials using new generation pumps and rapid-acting insulin analogues are needed.

1.3.3 Continuous glucose monitoring and sensor-augmented pump therapy

It is widely accepted that in order to reduce the fetal impact of maternal diabetes, periods of hyperglycaemia should be minimised. However, in doing so, the risk of hypoglycaemia may be increased (129). Given that pregnant women are especially prone to hypoglycaemia (9,11), fear of hypoglycaemia can also limit their ability to achieve near-normoglycaemia.

Continuous glucose monitoring devices (CGM) consist of a transcutaneous sensor that continuously measures interstitial glucose as a measure of blood glucose and a transmitter that either stores the data obtained by the sensor for retrospective analysis or transmits the glucose values to a receiver so that they can be seen by the user in real time. CGM therefore provides a more detailed description of glucose control than can be achieved with self-monitoring of capillary blood glucose (SMBG) via finger-stick measurements.

Users of CGM can see trends in glucose readings and set alerts for hyperglycaemia or hypoglycaemia that may be missed when relying on clinical symptoms and capillary glucose measurements alone (7,130). This allows for earlier intervention and potential avoidance of more severe glucose disturbances. In non-pregnant populations, CGM has been demonstrated to reduce HbA1c, glucose excursions and exposure to hyper- and hypoglycaemia (131–134).

Sensor-augmented pump therapy involves the user wearing both a CGM and an insulin pump. The glucose measurements obtained via CGM are entered into the pump (either automatically or manually) and, using inbuilt calculators, the pump can recommend appropriate insulin bolus and/or correction doses.

Treatment of type 1 diabetes using sensor-augmented pump therapy has been demonstrated to improve glycaemic control and reduce hypoglycaemia compared to

treatment using multiple daily injections of insulin or insulin pump therapy alone (135–139). The benefits of sensor-augmented pump therapy appear to be greatest with increased sensor use (134,136,139,140) and in patients who begin with higher HbA1c values (131,137,140).

Very few studies have examined the use of CGM devices or sensor-augmented pump therapy in pregnancy. To date, studies have demonstrated that CGM is accurate in pregnancy (13,141) and can assist in identification of hyperglycaemia and nocturnal hypoglycaemia (142,143), and allow more targeted treatment (143). The two earliest published randomised trials reported different outcomes – one suggested that CGM may result in lower HbA1c, lower birthweight percentiles and lower risk of macrosomia (144), and the other suggested no effect on glycaemic control or perinatal outcomes (145). A subsequent randomised trial of intermittent retrospective CGM (GlucoMOMS) in 304 pregnant women with diabetes (109 of whom had type 1 diabetes) found no difference in HbA1c or neonatal outcomes between women randomised to intermittent retrospective CGM and those in the control group who used only conventional glucose testing (146). The only difference observed between the two groups was a lower rate of pre-eclampsia in the CGM group (4% vs 12%, $p = 0.01$). The results of the two negative trials (145,146) are unsurprising given that both studies investigated the intermittent use of CGM. Outside of pregnancy, benefits are associated with use of CGM for at least 70% of the time (147,148) and as such intermittent use is not recommended (149).

Most recently, a large, multicentre, international randomised controlled trial of continuous real-time CGM (CONCEPTT) was conducted in 215 pregnant women with type 1 diabetes and a further 110 who were planning pregnancy (150). The study found no differences in outcomes between participants planning pregnancy who used CGM compared to those who used capillary glucose monitoring. However, among the pregnant participants, those using CGM spent more time with target glucose concentrations (68% vs 61%, $p = 0.003$), and had a 0.2% lower HbA1c at the end of the study than participants in the control group. Even with only modest improvements in glycaemic control, the odds ratios were approximately halved for large-for-gestational-

age, neonatal intensive care admissions lasting more than 24 hours, and neonatal hypoglycaemia in the offspring of the CGM group participants.

As in non-pregnant populations, CGM appears to be less accurate in periods of hypoglycaemia or when the glucose concentration is changing rapidly (e.g., during exercise) (13,141,151).

1.4 Closed-loop insulin delivery

1.4.1 Closed-loop system components

Closed-loop systems are automated insulin delivery systems that have three components: a glucose monitor, an insulin delivery device, and a control algorithm that is administered via a computer system (Figure 1.1). In modern systems, the glucose monitor is a continuous glucose monitor (CGM) that measures interstitial glucose. A glucose reading from the monitor is then transmitted to the algorithm device (a mobile phone or tablet computer), which calculates an appropriate insulin dose. An instruction is then sent to an insulin pump, which delivers insulin via a continuous subcutaneous insulin infusion (CSII).

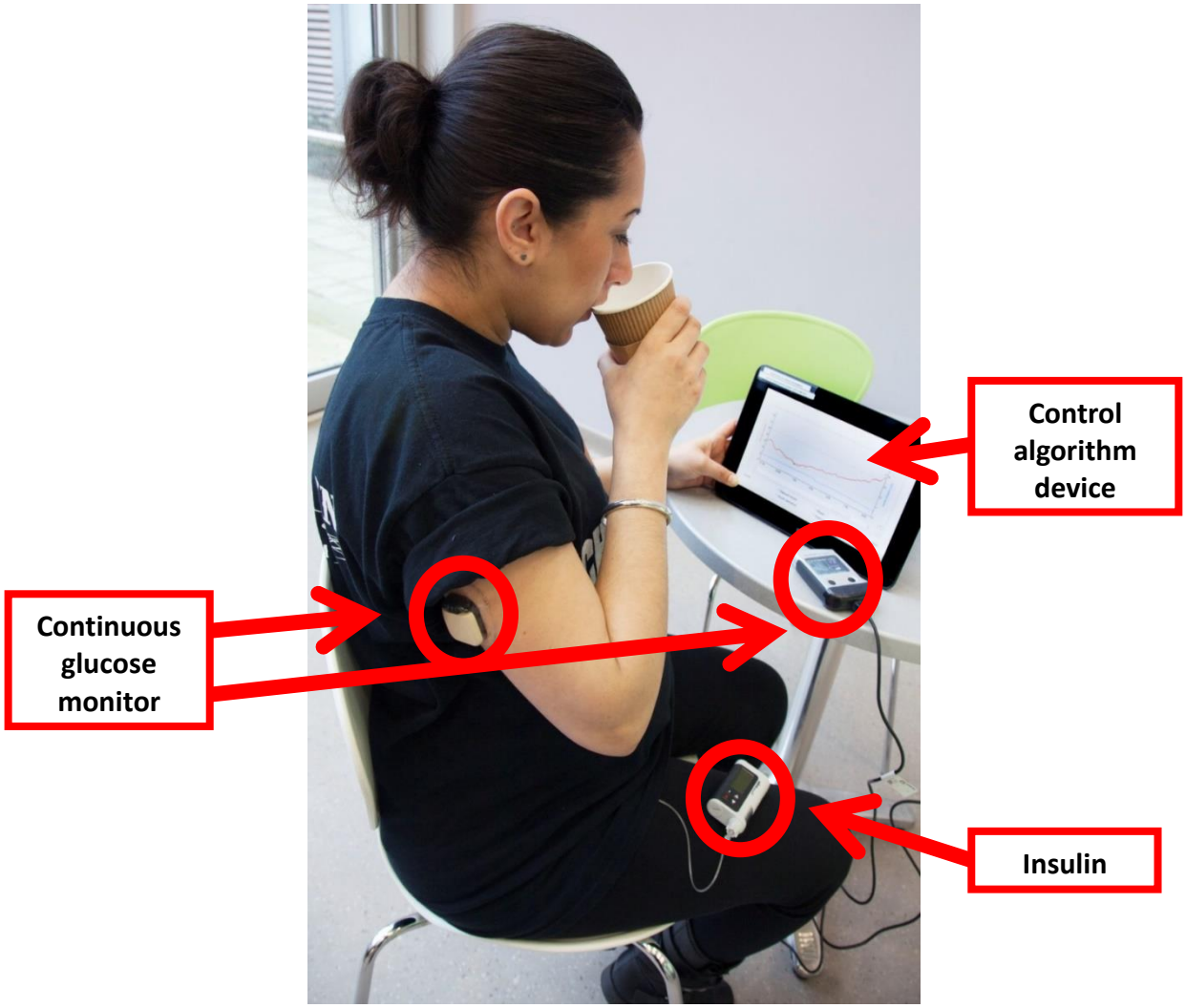


Figure 1.1: Components of a closed loop system: a) a continuous glucose monitor (sensor, transmitter and receiver); b) an insulin pump; and c) a control algorithm device.

1.4.2 Control algorithms

1.4.2.1 Proportional integral derivative

Proportional integral derivative (PID) algorithms control insulin administration using a combination of the proportional, integral, and derivative terms (152). These terms adjust insulin doses according to real time glucose concentration, the area under the curve between the actual and target glucose concentration, and rate of change of glucose to adjust insulin respectively. The three terms and three individualised constants determine the insulin dose administered. The PID algorithm reacts solely to measured glucose concentration and cannot predict future changes in glucose.

1.4.2.2 Model predictive control

Model predictive control (MPC) algorithms predict future glucose excursions based on patients' glycaemic responses to insulin and meals (153). The difference between the glucose concentration predicted by the model and a pre-set insulin target is used to determine the rate of insulin delivery. The majority of closed-loop systems currently under investigation use an MPC algorithm because these systems can account for meals, patient-initiated insulin boluses, and individual differences in insulin absorption more easily than systems using other algorithms.

1.4.2.3 Fuzzy logic

Fuzzy logic models recognise that the same dose of insulin may not always cause the same change in glucose concentration. These models aim to emulate the decision-making processes and expertise of clinicians and try to account for multiple possible responses to the same insulin dose. (154)

1.4.3 History of closed-loop systems

The concept of automated glucose control is not new. In the 1960s, a relatively simple "on-off" system of closed-loop glucose management using intravenous glucose and insulin was developed for use in research settings (155). This concept was further developed to incorporate a computational algorithm and the first commercial closed-loop system, the Biostator (Miles Laboratories, Elkhart, IN, USA), was released in 1977 (156). This system obtains blood via an intravenous catheter and measures the glucose concentration before discarding the sample. Blood glucose results are then fed to a computer algorithm that controls administration of intravenous insulin and dextrose. This large device is only suitable for use in closely-monitored inpatient settings and, despite multiple attempts, optimal glucose control could not be achieved with available algorithms (157).

Portable insulin pumps that deliver continuous subcutaneous infusions of insulin have been used in clinical care since the early 1980s (158). Since then, pump technology has continued to advance and is becoming increasingly popular. Improvements in insulin pump devices, availability of portable continuous glucose monitoring systems, and development of new quick-acting insulin analogues and more sophisticated control algorithms have accelerated the development of closed-loop systems.

One approach to closed-loop uses intraperitoneal insulin delivery with a glucose sensor either implanted in the superior vena cava (159) or inserted subcutaneously (160). This approach has the potential to reduce inherent delays in subcutaneous insulin absorption and deliver insulin in a way that more closely mimics normal physiology. However, intraperitoneal devices are expensive, require surgical implantation and carry a higher risk of infection and failure than subcutaneous pumps. Intraperitoneal pumps would be inappropriate for routine use during pregnancy.

All other closed-loop prototypes currently being investigated use a subcutaneous glucose measurement device coupled with continuous subcutaneous insulin infusion via a

portable pump. This subcutaneous-subcutaneous approach is attractive and likely represents the most feasible model because it is minimally invasive and uses devices that are already commercially available and acceptable by patients.

1.4.4 Progress to date

1.4.4.1 Low glucose and predictive low glucose suspend

The simplest forms of automated insulin delivery are low glucose and threshold suspend systems. In these systems, a message is sent to the insulin pump to temporarily stop basal insulin delivery when the CGM device detects (low glucose suspend) or predicts hypoglycaemia (predicted low glucose suspend) and there is no response to warning alarms. This feature has been demonstrated to decrease frequency, duration and severity of hypoglycaemia without causing hyperglycaemia or ketoacidosis (161–166).

Sensor-augmented pump systems with a low glucose suspend feature have been commercially available since 2009 (Paradigm Veo and MiniMed 530G with Enlite; Medtronic Diabetes, Northridge, CA, USA). They suspend insulin delivery for two hours based on measured hypoglycaemia but not predicted hypoglycaemia. In selected cohorts of high-risk patients, the Paradigm Veo can reduce exposure to hypoglycaemia without inducing hyperglycaemia (166,167). A predictive low glucose suspend system (MiniMed 640G; Medtronic Diabetes, Northridge, CA, USA) was commercially launched in 2015, and has been associated with a reduction in hypo- and hyper-glycaemic excursions (168).

The effects of low glucose and threshold suspend systems in pregnancy have not been evaluated.

1.4.4.2 Overnight closed-loop insulin delivery

Approximately 50% of severe hypoglycaemic episodes occur overnight and can therefore go unnoticed (169). The proportion of severe hypoglycaemic episodes that occur overnight is similar in pregnant and non-pregnant populations (35). However, in pregnancy, the risk of adverse outcome may be particularly high because counter-regulatory responses to hypoglycaemia are impaired and severe hypoglycaemia is more frequent (10).

One potential early application of closed-loop technology is overnight, when meals and exercise are less relevant so models for glucose control are less complex. Overnight closed-loop could also offer substantial clinical benefits including tighter glycaemic control and prevention of nocturnal hypoglycaemia.

The safety of overnight closed-loop glucose control using an MPC-based algorithm have been demonstrated in multiple non-randomised and proof of concept trials (170,171) and in randomised crossover studies examining children, adolescents and adults in inpatient and unsupervised home settings (172,173). In these studies, overnight-closed loop resulted in better glycaemic control and less exposure to hypoglycaemia, including after a large carbohydrate meal and alcohol (174). Over a two month period of 36 participants at home, overnight closed-loop use (from 2000 to 0800 hours) was associated with a modest reduction in HbA1c (-0.3% vs 0.2%, $p = 0.047$), with an increased time-in-target (66.7% vs 58.1%, $p < 0.001$) compared to sensor-augmented pump therapy (175).

Two small pilot studies have demonstrated that overnight closed-loop control using an MPC-based algorithm is safe in early and late pregnancy and can achieve near-normoglycaemia while reducing exposure to hypoglycaemia (13,14).

Closed-loop systems using PID and fuzzy logic algorithms have also been shown to be safe and able to maintain good overnight glycaemic control in small non-randomised inpatient studies (176–178) but have not been tested in pregnancy.

1.4.4.3 Day and night (24 hour) closed-loop

Ideally, closed-loop technology would be able to achieve and continuously maintain normoglycaemia autonomously including during exercise and meal times. However, this remains an ambitious goal. In conventional treatment, patients give a pre-meal insulin bolus to account for the food they are about to eat, allowing time for insulin absorption and action before glucose from the meal has reached the bloodstream. However, closed-loop control around meal times would rely on changes in interstitial glucose to detect meals, resulting in an inherent delay. These delays, together with the pharmacokinetics of currently available insulins, can result in initial post-meal hyperglycaemia with subsequent between meal hypoglycaemia.

Four proof of concept studies of day and night closed-loop control without meal announcement demonstrated that closed-loop could achieve acceptable glycaemic control with low rates of hypoglycaemia (154,176,179–181). As expected, in fully-automated closed-loop control, prolonged post-prandial hyperglycaemia persisted and post-prandial hypoglycaemia occurred frequently. Hypoglycaemia could be avoided in the first two hours after ingestion of a small meal (30 +/- 5 g carbohydrate) using an MPC algorithm with a safety constraint that accounts for insulin on board (180).

As an intermediate step to 24-hour fully-automated closed-loop control, some groups have proposed a system that provides day-and-night closed-loop control but relies on the user to input the timing, and in some cases carbohydrate content, of meals so that the algorithm can calculate appropriate bolus doses (182). One study found that peak post-prandial glucose concentrations were lower when a pre-meal priming insulin dose was given than when a fully automated closed-loop system was used (183). Other studies have utilised closed-loop technology for basal insulin delivery but have relied on

standard calculation and manual administration of pre-meal insulin boluses to control meal-related glucose excursions with good effect (160,171,173,184–186).

Hybrid closed-loop systems have been demonstrated to be safe, and to be associated with improved glucose control (reduced mean glucose or HbA1c, increased percentage time with target glucose concentrations), compared with baseline, pump or sensor-augmented pump therapy in a range of different populations including children, adolescents, and adults in supervised and unsupervised settings over periods of up to three months (173,182,185–194).

A randomised crossover study of 12 pregnant women examined the use of 24-hour closed-loop insulin delivery with standardised meals and exercise and manual administration of pre-meal boluses (14). In this study, closed-loop achieved near-normoglycaemia with less frequent severe hypoglycaemia than conventional insulin pump therapy.

Although preliminary, data from these studies suggest that stable glycaemic control can be achieved with day-and-night closed-loop insulin delivery. Meal times and exercise continue to pose the greatest challenges for achieving euglycaemia. Day-and-night use of closed-loop therapy has been demonstrated to be feasible in the outpatient setting (170) although definitive proof of clinical efficacy has not been established in routine care settings.

1.4.4.4 Dual hormone closed-loop systems

Under normal physiological conditions, glycaemia is largely regulated by feedback systems using insulin and glucagon. In people with type 1 diabetes, glucagon function is impaired (195), which increases risk of hypoglycaemia. Some investigators suggest that an artificial pancreas using both insulin and glucagon to control glucose would more closely mimic normal physiology and would therefore be better able to prevent

hypoglycaemia. Some investigators have demonstrated, under research conditions and in a diabetes camp setting, that dual hormones systems can provide good glycaemic control and reduced exposure to hypoglycaemia (191,196–200). In a randomised trial of a dual hormone (insulin and glucagon) closed-loop system, single hormone (insulin only) closed-loop system, and conventional insulin pump therapy in 40 participants over three 24 hour inpatient study visits, both closed-loop systems showed improved glycaemic control compared with conventional pump therapy, but there was no difference in percentage time-in-target between participants using the single vs dual hormone systems (201). Additionally, current formations of glucagon are unstable and would not be viable for use in routine outpatient settings (202). There have been no studies of dual hormone closed-loop systems in pregnant women.

1.4.5 Limitations and challenges for closed-loop systems

1.4.5.1 Sensor delay/inaccuracy

At present, the most viable option for commercial launch of a closed-loop insulin delivery system uses continuous glucose monitoring systems (CGM) that measure interstitial glucose as a marker of blood glucose. Although these monitoring systems have a level of accuracy that is safe, factors including calibration error and sensor drift can mean that glucose values measured by interstitial sensors are less accurate than capillary blood glucose measurements (203). Over-estimation of glucose is of particular concern because, if relied upon, these values would lead to excessive insulin doses and potentially hypoglycaemia.

Further, the time required for glucose to move from the blood to the interstitium creates a lag of approximately 6 minutes between blood glucose and interstitial glucose (204). While some control algorithms account for sensor inaccuracy and the known delay between blood and interstitial glucose, the closed-loop system ultimately relies on the glucose readings obtained via CGM to make calculations and adjust insulin doses.

1.4.5.2 Time to onset and peak of insulin activity

As with all automated control systems, there is a time lag between the point at which the algorithm makes a change and the point at which the effect of that change is realised. Most algorithms currently under investigation take into account the time required for delivery and absorption of insulin and the time to peak insulin activity. However, it can be difficult to accurately predict these times because absorption and action times of insulin vary considerably between different individuals and within the same individual at different times (198,205).

Our group previously described a significant gestational delay of approximately 30 minutes in time-to-peak plasma aspart concentration from early to late pregnancy (taking 80±30 minutes in late compared to 50±10 minutes in early pregnancy) (77). We also found marked inter-occasion variability of insulin pharmacokinetics during type 1 diabetes pregnancy, showing that, while basal insulin delivery was stable, the day-to-day variability of pre-meal boluses was particularly striking in late gestation (206).

To avoid accumulation of insulin and subsequent iatrogenic hypoglycaemia, closed-loop algorithms need to adjust glucose concentration gradually and take into account insulin that has already been administered but has yet to reach its full effect (207). Rapid acting insulin analogues including aspart and lispro have reduced insulin-related time lag (208,209), however can still take up to 90 minutes to reach maximum glucose-lowering effect (210). This is much longer than endogenous, secreted insulin, which peaks at 1-2 minutes after ingestion of meals (Figure 1.2).

Preliminary studies have found that mechanisms including site warming (211) and co-administration of hyaluronidase (212,213) can accelerate the pharmacokinetics of insulin while awaiting the development of ultra-rapid-acting insulin analogues.

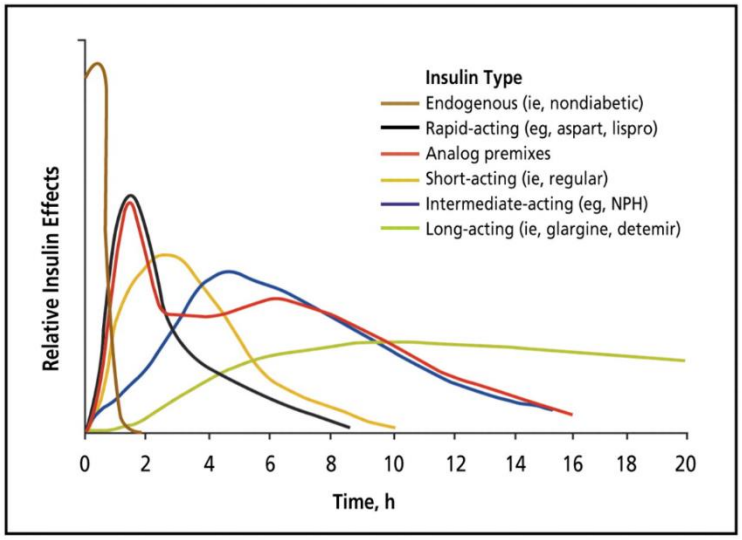


Figure 1.2: Pharmacokinetic profiles of endogenous insulin, human insulin, and insulin analogues. Reproduced from (214). Data for graph were extracted from US Pharmacist (215). Data for the endogenous curve were adapted from (216).

1.4.5.3 The algorithm, meals and exercise

Algorithms for closed-loop glucose control are now able to achieve near-optimal glycaemia overnight under controlled conditions. However, closed-loop insulin delivery after meals and exercise remains challenging. Where conventional management uses knowledge of food and activity to proactively adjust carbohydrate and insulin doses to minimise or mitigate glucose excursions, fully automated closed-loop systems rely on changes in interstitial glucose to identify meal times and exercise before the algorithm can respond and change the insulin infusion rate. While improvements in algorithms and adjunct tools like heart rate monitors can be used to identify meals and exercise early, without meal or exercise announcement, automated closed-loop systems are acting reactively rather than proactively.

Hybrid closed-loop systems that incorporate meal announcement or manual pre-meal boluses will likely provide the most feasible way forward until the challenges of

maintaining good glucose control during meal times and exercise without human intervention can be overcome. This is certainly the case in pregnancy, where gestational delays in glucose disposal and slower insulin pharmacokinetics mean that human intervention with pre-meal boluses 15 to 30 minutes before eating will be required until faster acting insulins are available.

1.5 Thesis outline

This thesis explores glycaemic control in pregnancies complicated by type 1 diabetes.

Chapter 2 details the results of the first randomised crossover trial of overnight closed-loop insulin delivery in 16 women with type 1 diabetes recruited at between eight and 24 weeks gestation. This study was designed to assess the safety, efficacy, and utility of overnight closed-loop in pregnancy. After recruitment, women were trained on the study devices before completing four weeks of treatment with sensor-augmented pump therapy and four weeks of treatment with sensor-augmented pump therapy with overnight closed-loop insulin delivery, in random order. After completion of the two study phases, women could continue with their diabetes treatment of choice until delivery.

In Chapter 3, I describe the first randomised crossover trial of day-and-night closed-loop insulin delivery in 16 women with type 1 diabetes. In this study, women were again recruited between eight and 24 weeks gestation and completed two study arms in random order. In the first study arm, they used sensor-augmented pump therapy and in the other study arm they used closed-loop insulin delivery continuously. Women in this study were able to continue with their diabetes treatment of choice from the end of the study phases up until six weeks post-partum.

Chapter 4 details the experiences of women who participated in the overnight study of closed-loop insulin delivery detailed in Chapter 2. Using semi-structured interviews and the Diabetes Technology Questionnaire and Hypoglycaemia Fear Survey II, we were able to explore the experiences of pregnant women with type 1 diabetes, and the relationships between perceptions of glucose control, attitudes to technology, and glycaemic responses with regard to closed-loop insulin delivery.

In Chapter 5, I present an observational study of the 27 women who chose to continue using closed-loop insulin delivery during their labour and delivery after participation in the crossover trials described in Chapter 2 and Chapter 3.

Chapter 6 describes an observational study of detailed CGM glucose measurements in 16 mother-infant pairs.

Chapter 7 summarises the findings of each of the studies and includes a discussion of strengths, limitations, and the contribution to knowledge from these studies. I conclude by discussing ongoing clinical challenges and future research directions.

2. Overnight closed-loop insulin delivery in pregnancy

2.1 Background

Complications of type 1 diabetes mellitus during pregnancy include increased rates of congenital anomaly, stillbirth, neonatal death, preterm delivery, and macrosomia (1). Congenital anomalies are associated with poor maternal glycaemic control around the time of conception, whereas the other complications are associated with maternal hyperglycaemia that persists during pregnancy (1–4,36).

Pregnant women with type 1 diabetes face particular challenges in trying to maintain tight glycaemic control. Insulin requirements typically increase by a factor of 2 to 3 during the second and third trimesters, with substantial day-to-day variability, making the need for dose adjustments and their required magnitude unpredictable (6,78). Even with regular glucose monitoring, intensive insulin therapy, and HbA1c levels below 7%, pregnant women with type 1 diabetes have glucose concentrations above the target range approximately half the time (7,8). They also have increased rates of hypoglycaemia (6,9–11), with glucose concentrations that are below the target range for up to 3.5 hours per day (8), so the benefit of avoiding hyperglycaemia for the infant must be weighed against the risk of hypoglycaemia for the mother.

Technological advances in glucose monitoring and insulin delivery including continuous glucose monitoring, insulin pumps, and sensor-augmented pump therapy may allow for safer improvements in glycaemic control (12). Closed-loop systems use a computer algorithm (a set of mathematical instructions) to adjust insulin-pump delivery in response to glucose measurements obtained from real-time continuous glucose monitors (217). These systems have been shown to improve glycaemic control without increasing the risk of hypoglycaemia under experimental conditions (174,218,219), in trials of supervised outpatient treatment (170,180,191,192,220), and in studies of unsupervised, self-administered treatment among patients who were not pregnant (173,221,222). Preliminary data suggest that closed-loop systems may maintain near-normal glucose control and minimise the risk of nocturnal hypoglycaemia among pregnant women with type 1 diabetes (13,14). In this chapter, I present a 4-week, randomised, crossover trial of an overnight closed-loop system, followed by a 14-week continuation phase of day-and-night closed-loop therapy. This study encompassed pregnancy-related challenges, including antenatal hospital admission, labour and delivery, and postnatal adaptation.

2.2 Aim

To assess the feasibility, utility, safety, and efficacy of overnight closed-loop insulin delivery in pregnant women with type 1 diabetes.

2.3 Methods

2.3.1 Study participants

We recruited pregnant women with a history of type 1 diabetes mellitus for at least 12 months. Participants were 18 to 45 years of age, with a pregnancy of between 8 and 24

weeks of gestation and an HbA1c level between 6.5 and 10.0%. The women were receiving intensive insulin therapy administered by means of either multiple daily injections or an insulin pump. Women were excluded if they had conceived with the use of assisted reproductive technologies, were receiving concurrent treatment that might influence glucose control, had a total daily dose of insulin >1.5 units per kilo, had a body mass index (BMI) >45 kg/m², had a multiple-gestation pregnancy, had clinically significant nephropathy, neuropathy, or proliferative retinopathy, as judged by the investigator, or were unable to communicate in English. All participants provided written informed consent.

2.3.2 Study oversight

The study was approved by the East of England Research Ethics Committee of the Health Research Authority, with notification of no objection provided by the U.K. Medicines and Healthcare Products Regulatory Agency. The study was overseen by an independent data and safety monitoring board.

Abbott Diabetes Care provided discounted continuous glucose monitoring devices and consumables. Company representatives had no role in the design of the study; in the collection, handling, analysis, or interpretation of data.

2.3.3 Study design

The study was an open-label, multicentre, randomised, crossover trial. Participants were recruited from three U.K. National Health Service (NHS) sites.

After enrolment, participants were trained to use the study devices: a DANA Diabecare R Insulin Pump (SOOIL) and the FreeStyle Navigator II (Abbott Diabetes Care). After a run-in period of 2 to 4 weeks for device training and optimisation of insulin doses,

participants were randomly assigned, in permuted blocks of 4, to either the overnight closed-loop system (intervention) or sensor-augmented pump therapy (control). Participants underwent a 2-week washout period after completing the first assigned intervention and before starting the second intervention. During the washout phase, participants used capillary blood glucose monitoring with or without continuous glucose monitoring or pump therapy but could not use the closed-loop system.

After completion of the randomly assigned interventions, participants could choose to continue sensor-augmented pump therapy or the day-and-night closed-loop system with manually administered boluses before meals until delivery. This continuation phase provided a longer-term feasibility assessment of 24-hour closed-loop therapy while addressing the ethical questions that would be raised by withdrawal of an effective treatment during pregnancy.

All participants used rapid-acting insulin analogues, either aspart or lispro. Participants were advised to perform capillary glucose testing at least seven times a day, with standard glucose targets in both groups (3.5 to 5.5 mmol/L before a meal and <7.8 mmol/L 1 hour after a meal). Routine antenatal clinic visits were scheduled every two weeks, with fetal ultrasonographic assessments performed at 12, 20, 28, 32, and 36 weeks of gestation. There were no restrictions on physical activity, meals, or overseas travel, and no remote monitoring was performed. Participants had access to a 24-hour telephone line for assistance with technical difficulties.

C-peptide levels were measured at baseline and when the serum glucose concentration was within the target range (3.5 to 7.8 mmol/L), and HbA1c levels were measured at baseline, after each intervention phase, and at 28, 32, and 36 weeks of gestation at a single central laboratory.

2.3.4 Closed-loop system

During closed-loop therapy, a computer program, housed on a tablet computer, used continuous glucose measurements to determine an appropriate insulin dose. The basal insulin was delivered automatically by means of an insulin pump every 12 minutes (Figure 2.1). Pre-prandial boluses were administered manually (15 to 30 minutes before the meal) as clinically indicated (77). To initialise closed-loop therapy, the participant's weight and total daily insulin dose were entered in the computer program. During the 4-week randomised phase, participants started closed-loop therapy after their evening meal and stopped before breakfast. During the day-and-night continuation phase, closed-loop therapy was used continuously, with manually administered boluses before meals. Safety rules limited maximum insulin dose and suspended insulin delivery when the glucose concentration was falling rapidly and/or <4.3 mmol/L. The device had to be within approximately 30 metres of the participant in order to maintain connectivity. There were no programming changes in anticipation of antenatal glucocorticoid use, labour, or delivery.

Figure 2.1: Participant wearing the closed-loop system

2.3.5 Study endpoints

The primary efficacy end point was the percentage of time that glucose was in the target range of 3.5 to 7.8 mmol/L overnight, as recorded by means of continuous glucose monitoring during each four-week study phase. Secondary efficacy outcomes were:

- Percentage time spent with sensor glucose <3.5 mmol/L to quantify borderline hypoglycaemia
- Percentage time spent with sensor glucose ≤2.8 mmol/L to quantify moderate hypoglycaemia
- Percentage time spent with sensor glucose >7.8 mmol/L to quantify the duration of hyperglycaemia
- Percentage time spent with sensor glucose >10.0 mmol/L to quantify significant hyperglycaemia
- Percentage time spent with sensor glucose >3.5 to ≤10.0 mmol/L to quantify near optimal target range
- Area under the curve (AUC) for sensor glucose >7.8 mmol/L, >6.7 mmol/L, <3.5 mmol/L, and <2.8 mmol/L
- Percentage time CGM worn to quantify compliance
- Low blood glucose index to quantify the risk of hypoglycaemia
- Standard deviation of the rate of change of CGM to quantify the glucose variability
- Insulin delivered (basal, bolus, and total) to assess insulin needs
- HbA1c and, average CGM to quantify glucose control
- Episodes of severe hypoglycaemia requiring assistance
- Mild-moderate episodes of hypoglycaemia <3.5 mmol/L (mild) and <2.8 mmol/L (moderate) for 20 minutes duration
- Nocturnal hypoglycaemia: CGM glucose <3.5 mmol/L (mild) and <2.8 mmol/L (moderate) between 23:00 and 07:00 hours

Safety endpoints included the number and duration of hypoglycaemic episodes (moderate or severe). Moderate hypoglycaemia was defined as a glucose concentration of less than 3.5 mmol/L for 20 minutes or longer, as measured by continuous glucose monitoring. A severe hypoglycaemic episode was defined as an episode requiring third-party assistance.

The feasibility of day-and-night closed-loop therapy in the continuation phase (from the end of the crossover phase until delivery) was assessed on the basis of glucose measurements during sequential four-week intervals and over the period as a whole. The same glucose targets and study endpoints were used during the crossover and continuation study phases.

2.3.6 Statistical analysis

In our previous study of a closed-loop system with the use of sensor-augmented pump therapy in pregnant women with type 1 diabetes (median HbA1c 6.4%), the mean (±SD) percentage of time that glucose concentrations were in the target range was 61.7±24.9% (14). We calculated that we would need to enrol 16 women for the current study to have a power of 80% to detect a 30% relative increase in the percentage of time that glucose concentration was in the target range (from 62% with sensor-augmented pump therapy to 80% with the closed-loop system), at an alpha level of 0.05 (two-tailed). The standard deviation for the primary outcome was assumed to be 25% (13,14).

Statistical analyses were performed on an intention-to-treat basis, with data analysed according to the study phase to which the participant had been assigned, regardless of adherence to the assigned intervention. We used linear mixed-effects models to estimate the percentage of overnight time that the glucose concentration was in the target range (response variable). The fixed effect of interest was whether there was a difference between sensor-augmented pump therapy and closed-loop therapy. Since the response variable was a repeated measure, we included nested random effects for the average time-in-target value for each study participant and for each 4-week time period for each

participant. The fit of the model was not improved by including a term for either study phase-by-intervention interaction or autocorrelation of the response variable over time, and the estimated difference between study phases was not materially altered. Functional analysis of the continuous glucose data (223) was performed and adjusted for weeks of gestation and period effect. Sequential glucose measurements were modeled as trajectories by calculating continuous mathematical functions of glucose measurements. These trajectories were modeled by fitting B-splines to the repeated measures (224). A two-sided significance level of 0.05 was used for both primary and secondary outcomes, without adjustment for multiple comparisons.

2.4 Results

2.4.1 Study participants

Twenty participants were recruited to the study. Of these, three withdrew during the run-in training phase and 17 participants were randomised. One participant withdrew during her first study phase (sensor-augmented pump therapy) because of termination of pregnancy for trisomy 13 (a chromosomal anomaly unrelated to diabetes). Sixteen participants completed both study arms and are included in the analyses (Table 2.1). Six participants were using multiple daily insulin injections and 14 participants were continuous glucose monitoring naïve prior to the study.

Table 2.1: Baseline characteristics of study participants

Baseline characteristics (N=16)	**Number (%)**	**Mean (SD)**
Age (years)		34.1 (4.6)
BMI (kg/m^2)		29.7 (5.7)
HbA1c (%)		6.8 (0.6)
Booking HbA1c >7.5% (58 mmol/mol)	2 (13)	
Duration of diabetes (years)		23.6 (7.2)
Pump use prior to study	10 (63)	
CGM use prior to study	2 (13)	
Total daily insulin dose (units)		52.8 (18.1)
		[0.55 units/kg]
Baseline euglycaemic c-peptide level		
(pmol/L; median [interquartile range])		20 (10,37)
Weeks gestation*		14 (3.3)
		[range 9 – 20.2]
Primiparous±	7 (44)	
Recruitment site		
- Cambridge	10 (63)	
- Norwich	5 (31)	
- Ipswich	1 (6)	

*Weeks gestation at randomisation. Randomisation was performed after recruitment and 2 to 4 weeks of device training when insulin regimens were optimised and participants were competent in using the study devices.
±Among the nine women with previous pregnancies, there were five with previous pregnancy losses (five miscarriages and two stillbirths), one with a second trimester termination of pregnancy for major malformation, and two with early preterm deliveries (before 34 weeks gestation).

2.4.2 Study Outcomes

The percentage of overnight time participants spent with glucose values within the target range was significantly greater during closed-loop than during sensor-augmented pump therapy (74.7 vs 59.5, absolute difference 15.2 percentage points, $CI_{95\%}$=6.1 to 24.2; p=0.002; Figure 2.2, Table 2.2). The mean glucose was significantly lower during closed-loop, both overnight (6.6 vs 7.4 mmol/L, p=0.009; Table 2.2) and across 24 hours (7.1 vs 7.6 mmol/L, p<0.0001; Tables 2.2 and 2.3). While 12 participants had a higher percentage time-in-target during closed-loop therapy than during sensor-augmented pump therapy, 4 participants did not (i.e., they had equal or lower percentage time-in-target during closed-loop compared with during sensor-augmented pump therapy; Table 2.8).

The incidence of maternal hyperglycaemia was lower during closed-loop than during sensor-augmented pump therapy both overnight and across 24 hours. The incidence of substantial nocturnal hyperglycaemia (glucose concentration >10 mmol/L) was significantly lower during overnight closed-loop compared to sensor-augmented pump therapy (Table 2.2). Functional data analysis demonstrated that overnight closed-loop was associated with a significantly lower glucose for a total time of 7 hours and 20 minutes (between 01.50-09.20 hours) with no significant impact of gestational age or period (Figure 2.3).

The percentage of time spent hypoglycaemic (<3.5 mmol/L) was low (<2%) with no significant differences between the two phases. There were no episodes of severe hypoglycaemia during either study phase.

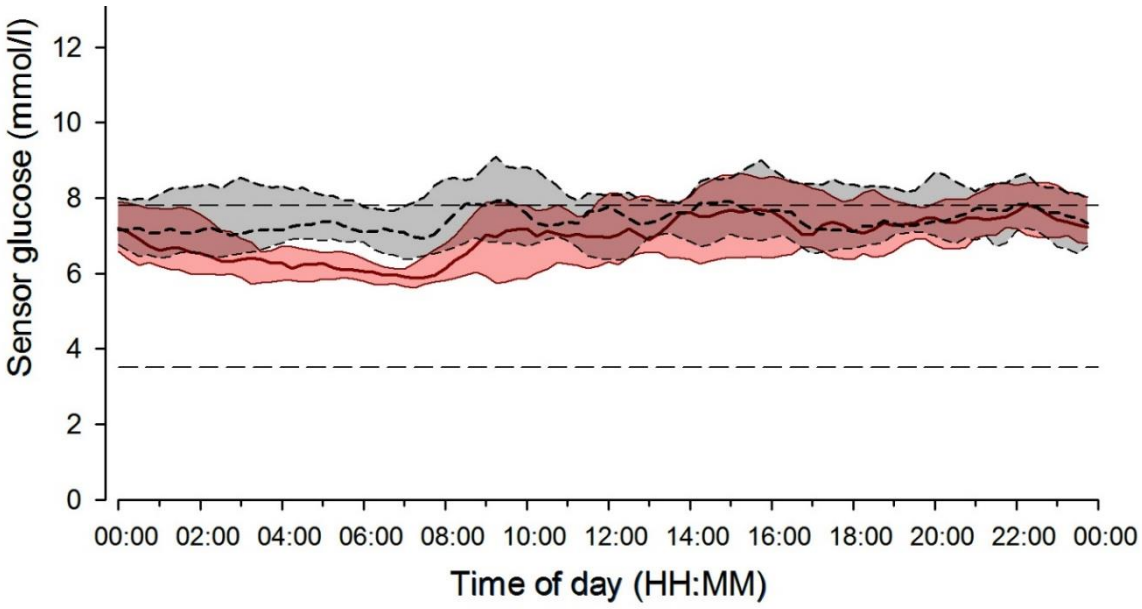


Figure 2.2: Median sensor glucose values and interquartile ranges over 24 hours in sensor-augmented pump therapy and closed-loop interventions. Sensor-augmented pump therapy phase shaded in grey, overnight closed-loop phase shaded in red. The pregnancy target range is 3.5-7.8 mmol/L.

Table 2.2: Comparison of sensor-augmented pump therapy and closed-loop automated insulin delivery during the overnight period (2300-0700hrs) for the crossover phases of the study. The values reported are derived from linear mixed effects models.

	Sensor-augmented pump therapy	**Closed-loop**	**Absolute difference ($CI_{95\%}$)**	**P value**
Overnight (2300hrs-0700 hours)				
Time in target[*] (3.5-7.8 mmol/L)(%)	59.5	74.7	15.2 (6.1 to 24.2)	0.002
Time above target (%)	38.6	24.0	-14.5 (-24.2 to -4.9)	0.005
Time with glucose concentration above 10 mmol/L (%)	15.7	7.4	-8.3 (-13.7 to -3.0)	0.004
Time below target (%)	1.9	1.3	-0.6 (-1.7 to 0.6)	0.28
Time with glucose concentration below 2.8 mmol/L (%)	0.6	0.3	-0.2 (-0.9 to -0.4)	0.45
Number of hypoglycaemic events (Median [range]; <3.5 mmol/L for≥20 minutes)	2.5 (0-15)	3 (0-6)		0.68
Low blood glucose index[±]	1.3	1.3	0.1 (-0.4 to 0.5)	0.78
Mean glucose (mmol/L)	7.4	6.6	-0.8 (-1.3 to -0.2)	0.009
Area under the curve: (median [interquartile range])				
- glucose >7.8 mmol/L	147.7 (40.2-322.4)	39.2 (9.9-142.2)		0.07
- glucose >6.7 mmol/L	383.8 (222.0-608.9)	169.6 (98.5-413.7)		0.04
- glucose <3.5 mmol/L	0	0		
- glucose <2.8 mmol/L	0	0		
Standard deviation of sensor glucose (mmol/L)	1.5	1.4	-0.1 (-0.2 to 0)	0.13

[*] The primary efficacy endpoint was the percentage of time that glucose was in the target range of 3.5-7.8 mmol/L overnight, as recorded by CGM during each four week study phase. The percentage time above target refers to the time that the glucose concentration was above 7.8 mmol/L and percentage time below target to the time that the glucose concentration was lower than 3.5 mmol/L.
[±]The low blood glucose index assessed the duration and extent of hypoglycaemia.

Table 2.3: Comparison of sensor-augmented pump therapy and closed-loop automated insulin delivery during the day and night of the crossover phase of the study. The closed-loop system was only active overnight during this phase of the study and pre-meal boluses were given manually (15-30 minutes before eating). The values reported are derived from linear mixed effects models

	Sensor-augmented pump	**Closed-loop**	**Absolute difference ($CI_{95\%}$)**	**P value**
Day and night during crossover phase				
Time in target[*] (3.5-7.8 mmol/L) (%)	56.8	66.3	9.4 (5.1 to 13.8)	<0.001
Time above target (%)	40.9	31.6	-9.4 (-13.7 to -5.0)	<0.001
Time with glucose above 10 mmol/L (%)	17.3	12.6	-4.7 (-7.3 to -2.1)	0.001
Time below target (%)	1.8	1.9	0.1 (-0.3 to 0.5)	0.67
Time with glucose below 2.8 mmol/L (%)	0.33	0.39	0.05 (-0.1 to 0.2)	0.52
Number of hypoglycaemic events (Median [range]; <3.5 mmol/L for ≥20 minutes)	12 (2-26)	11 (0-37)		0.19
Mean glucose (mmol/L)	7.6	7.1	-0.5 (-0.8 to -0.2)	<0.001
TDD insulin (units/day)	58.2	59.8	1.7 (-6.9-10.2)	0.67
Sensor wear (hours)	20.6	21.1	0.5 (-1.0-2.0)	0.47

[*]The percentage of time that glucose was in the target range of 3.5-7.8 mmol/L over the 24-hour day and night period, as recorded by CGM during each four week study phase. The percentage time above target refers to the time that the glucose concentration was above 7.8 mmol/L and percentage time below target to the time that the glucose concentration was lower than 3.5 mmol/L.

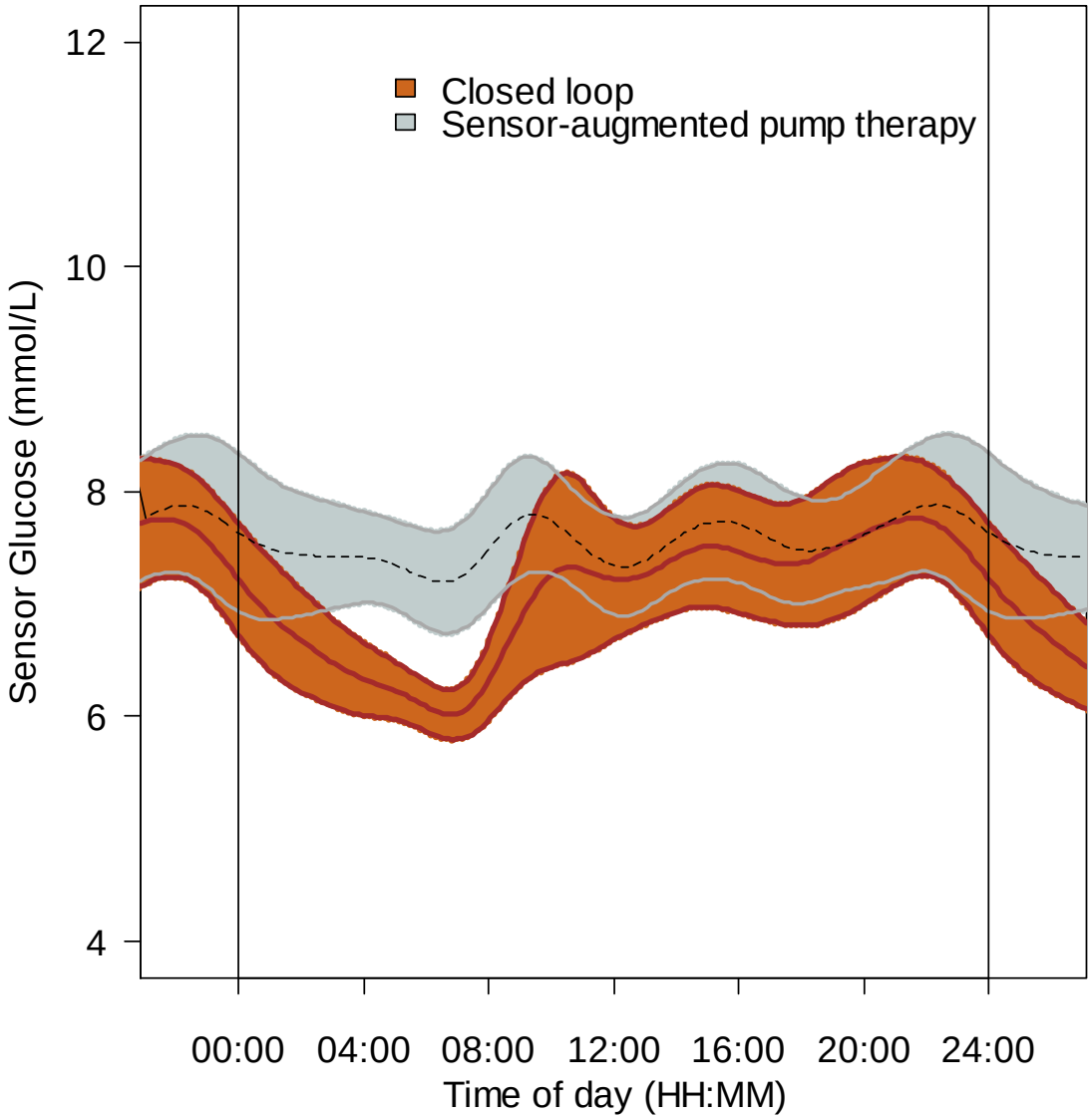


Figure 2.3: Mean sensor glucose values and 95% confidence intervals over 24hrs in sensor-augmented pump therapy (grey) and overnight closed-loop (red) randomised crossover phase of study. Graph derived from functional data analyses

Functional data analyses confirmed statistically significant differences in glucose control for a total time of 7 hours and 20 minutes (from 01.50 hours to 09.20 hours) with no impact of gestation and no period effect.

HbA1c levels declined from baseline to the end of both phases, with no significant difference in changes between the study periods (p=0.67). Participants used similar total daily insulin doses across both study phases, although, insulin delivery was significantly more variable during closed-loop (p<0.0001; Table 2.4). There were no differences in results between experienced pump users and pump-naïve participants (Table 2.5).

Table 2.4: Insulin doses during the sensor-augmented pump therapy and overnight closed-loop randomised crossover study

	Sensor-augmented pump therapy	**Closed-loop**	**p-value**
Overnight (23.00-07.00 hours)			
Total daily dose (units/night)	10.5	10.2	0.79
Basal (units/night)	9.0	9.4	0.63
Bolus (units/night)	1.6	0.9	0.05
Standard deviation of basal insulin (units)	0.2	0.8	<0.0001
Day and night			
Total daily dose (units/24hrs)	61.5	58.5	0.46
Basal (units/24hrs)	28.1	28.8	0.88
Bolus (units/24hrs)‡	33.2	31.2	0.58
Standard deviation of basal insulin (units)	0.2	0.7	<0.0001

‡Pre-meal boluses were given manually (15-30 minutes before eating) as clinically indicated.

Table 2.5: Glycaemic control during the randomised crossover study in participants who were using multiple daily injections (MDI) vs insulin pump therapy at enrolment

	Previous MDI users (*n*=6)			**Previous Pump users (*n*=10)**		
	Sensor-augmented pump	**Closed-loop**	**Difference (CL-SAP)**	**Sensor-augmented pump**	**Closed-loop**	**Difference (CL-SAP)**
% Time in target (3.5-7.8 mmol/L) overnight	66.0	78.8	15.8	58.3	73.8	16.9
Mean glucose overnight (mmol/L)	7.0	6.5	-0.5	7.4	6.6	-0.8
Median episodes of nocturnal hypoglycaemia‡	3.5	2.5	-1	3	2	-1

‡Hypoglycaemia episodes were defined as below 3.5 mmol/L for ≥20 mins

2.4.3 Adverse events

There were 26 adverse events (14 skin reactions, 12 minor illnesses), with no significant difference between study phases. There were 95 device deficiencies (18 during sensor-augmented pump therapy, 21 during closed-loop, 56 during run in and continuation phases). There were eight serious adverse events. One such event, a hospital admission in the closed-loop arm following an episode of self-treated hypoglycaemia due to recurrent vomiting, occurred during the randomised crossover trial; however, this occurred in the daytime, when closed-loop was not operational. Another serious adverse event (vomiting due to gastroenteritis) occurred during the run-in training phase and six more occurred during the feasibility phase (Table 2.6). No serious adverse events were considered by investigators to be device-related.

Table 2.6: Serious adverse events

Event number	Study phase	Device-related	Description
1	Run in	No	Admitted with 1 day of vomiting - likely gastroenteritis, no diabetic ketoacidosis. Good response to anti-emetics. Participant withdrew from study prior to randomisation due to a change in personal circumstances (moving out of area).
2	Closed-loop arm	No	Admitted with hypoglycaemia in the context of persistent vomiting diagnosed as viral gastroenteritis. Participant was unable to raise her blood glucose sufficiently using oral treatments (because of vomiting) and treated herself with glucagon before attending the Accident and Emergency Department. She did not require third party assistance. She was in the overnight closed-loop study phase but was using sensor-augmented pump therapy without closed-loop. This event occurred during the daytime, hence she had not yet turned on the closed-loop system.
3	Sensor-augmented pump arm	No	Congenital anomaly detected on routine anomaly scan (identified as trisomy 13 on subsequent genetic testing). Participant was withdrawn from the study and subsequently had a termination of pregnancy.
4	Follow up (day and night closed-loop)	No	Admitted for 24 hours to investigate threatened labour (later diagnosed as Braxton Hicks contractions). She remained on closed-loop throughout her hospital admission.
5	Follow up (day and night closed-loop)	No	Spontaneous rupture of membranes at 30 weeks gestation and admitted for antenatal steroids. She continued closed-loop during steroid administration, and throughout labour and delivery.
6	Follow up (day and	No	Admitted with preeclampsia at 23+5 weeks gestation. She was treated with antenatal steroids and continued closed-

	night closed-loop)		loop. She remained an inpatient until delivery at 28+2 weeks gestation. She has rheumatoid arthritis, coeliac disease, hypertension and Factor V Leiden thrombophilia. She had no history of a successful pregnancy (previous miscarriage and stillbirth).
7	Follow up (day and night closed-loop)	No	Admitted with pre-eclampsia at 34+4 weeks gestation. She used sensor-augmented pump therapy and closed-loop while in hospital. She was treated with anti-hypertensives and antenatal steroids before delivery caesarean-section at 35+1 weeks gestation.
8	Follow up (day and night closed-loop)	No	Admitted for investigation of hypertension and malaise at 32+3 weeks gestation. She used both sensor-augmented pump and closed-loop while in hospital.

2.4.4 Day and night closed-loop follow up

Fourteen participants chose to continue using closed-loop after finishing the crossover studies providing up to an additional 14.4 weeks of day-and-night closed-loop use for feasibility assessment. Participants maintained a median glucose of 6.9, 7.1, 6.9, and 6.4 mmol/L at 24-28, 28-32, 32-36 and >36 weeks gestation respectively (Tables 2.7 and 2.8). Median time spent with target glucose concentration was 70.9, 67.6, 67.8, and 77.3% at 24-28, 28-32, 32-36, and >36 weeks gestation. The median time spent hypoglycaemic was 1.2-2.1% throughout pregnancy.

Table 2.7: Day and night glucose measurements during the 24-hour closed-loop continuation phase, until delivery; median (interquartile range)

	24-28 weeks gestation (*n* = 14)	**28-32 weeks gestation (*n* = 12)**	**32-36 weeks gestation (*n* = 13)**	**36+ weeks gestation (*n* = 9)**
Percentage time in target‡	70.9 (63.8, 76.5)	67.6 (62.2, 73.7)	67.8 (66.0, 79.4)	77.3 (72.4, 83.6)
Percentage time above target	27.7 (22.4, 35.7)	30.8 (25.7, 35.7)	30.6 (19.2, 31.4)	20.7 (16.4, 25.4)
Percentage time below target	1.2 (0.4, 1.8)	1.2 (0.5, 1.6)	1.5 (0.8, 2.1)	2.1 (0.5, 2.4)
Mean glucose (mmol/L)	6.9 (6.6, 7.3)	7.1 (6.8, 7.4)	6.9 (6.5, 7.1)	6.4 (6.5, 6.6)

‡The time in target is defined as 3.5-7.8 mmol/L, time above target as >7.8 mmol/L and time below target as <3.5 mmol/L.

Table 2.8: Glycaemic control measures by participant during the randomised crossover study and follow up phase

Participant number	Measure	SAP study	Closed-loop	24-28 weeks	28-32 weeks	32-36 weeks	36 weeks+
1	**% time in target (3.5-7.8 mmol/L)**	46.4	44.7	44.2	54.3	55	69.8
	% time >7.8 mmol/L	52.3	55.2	55.5	45.2	43.3	27.9
	% time <3.5 mmol/L	1.2	0.0	0.3	0.5	1.7	2.3
	Mean glucose (mmol/L)	8.3	8.7	8.7	8.2	7.8	7.1
	HbA1c (mmol/mol / %)		52/6.9		53/7.0		
2	**% time in target (3.5-7.8 mmol/L)**	58.5	70.3	76.4		67.6	84.9
	% time >7.8 mmol/L	39.7	27.9	23.1		31.4	13.0
	% time <3.5 mmol/L	1.8	1.8	0.4		0.9	2.1
	Mean glucose (mmol/L)	7.3	6.8	6.7		7.1	6.1
	HbA1c (mmol/mol / %)	48/6.5	50/6.7	48/6.5	49/6.6	52/6.9	
3	**% time in target (3.5-7.8 mmol/L)**	46.7	59.1	61.0	54.9	64.1	
	% time >7.8 mmol/L	52.9	50.5	38.5	45.1	35.8	
	% time <3.5 mmol/L	0.4	0.4	0.5	0	0.1	
	Mean glucose (mmol/L)	8.0	7.5	7.5	7.8	7.4	
	HbA1c (mmol/mol / %)	52/6.9	54/7.1	54/7.1	56/7.3		
4[†]	**% time in target (3.5-7.8 mmol/L)**	36.0	58.6	71.2	71.1	76.2	77.3
	% time >7.8 mmol/L	63.8	40.9	28.8	28.6	23.0	22.6
	% time <3.5 mmol/L	0.2	0.5	0	0.3	0.8	0.1
	Mean glucose (mmol/L)	8.9	7.6	7.0	7.0	6.7	6.6
	HbA1c (mmol/mol / %)	43/6.1	38/5.6	41/5.9	43/6.1	44/6.2	
5[*†]	**% time in target (3.5-7.8 mmol/L)**	69.1	68.7				

	% time >7.8 mmol/L	29.3	29.1				
	% time <3.5 mmol/L	1.6	2.3				
	Mean glucose (mmol/L)	6.9	6.9				
	HbA1c (mmol/mol / %)	40/5.8	43/6.1	40/5.8			
6†	**% time in target (3.5-7.8 mmol/L)**	64.3	75.9	77.3	65.9	66.0	68.4
	% time >7.8 mmol/L	32.0	21.0	20.1	32.0	30.6	25.4
	% time <3.5 mmol/L	3.7	3.1	2.6	2.0	3.4	6.2
	Mean glucose (mmol/L)	6.9	6.5	6.3	7.2	6.9	6.4
	HbA1c (mmol/mol / %)	43/6.1	40/5.8				
7	**% time in target (3.5-7.8 mmol/L)**	52.5	71.3	62.9		80.8	
	% time >7.8 mmol/L	44.8	28.1	36.8		19.2	
	% time <3.5 mmol/L	0.5	0.5	0.3		0	
	Mean glucose (mmol/L)	8.0	7.0	7.3		6.5	
	HbA1c (mmol/mol / %)	50/6.7	49/6.6	53/7.0	52/6.9		
8†	**% time in target (3.5-7.8 mmol/L)**	52.9	62.3	70.7	80.3	72.1	
	% time >7.8 mmol/L	44.8	35.3	27.9	18.3	25.4	
	% time <3.5 mmol/L	2.3	2.3	1.5	1.5	2.5	
	Mean glucose (mmol/L)	7.9	7.2	6.9	6.4	6.6	
	HbA1c (mmol/mol / %)	59/7.5	50/6.7	48/6.5	47/6.5		
9‡	**% time in target (3.5-7.8 mmol/L)**	62.5	69.9	81.1	71.5		
	% time >7.8 mmol/L	34.4	26.4	17.0	28.0		
	% time <3.5 mmol/L	3.1	3.7	2.0	0.4		
	Mean glucose (mmol/L)	7.1	6.7	6.1	6.8		
	HbA1c (mmol/mol / %)	34/5.4	45/6.3	34/5.4			
10†	**% time in target (3.5-7.8 mmol/L)**	76.3	93.7	77.6	83.2	86.6	92.9
	% time >7.8 mmol/L	20.5	13.8	19.3	15.9	11.4	3.9
	% time <3.5 mmol/L	3.1	2.5	3.1	0.9	2.1	3.2
	Mean glucose (mmol/L)	6.4	6.0	6.3	6.3	6.0	5.5

	HbA1c (mmol/mol / %)	38/5.6	44/6.2	37/5.5			
11[‡†]	**% time in target (3.5-7.8 mmol/L)**	54.1	57.2	66.4	67.4	67.0	77.1
	% time >7.8 mmol/L	44.1	41.6	32.2	30.1	31.0	20.5
	% time <3.5 mmol/L	1.7	1.2	1.4	2.5	1.9	2.4
	Mean glucose (mmol/L)	7.7	7.8	7.1	7.0	6.9	6.4
	HbA1c (mmol/mol / %)	43/6.1	49/6.6	45/6.3		44/6.2	
12[‡]	**% time in target (3.5-7.8 mmol/L)**	46.3	46.9	55.5	58.9	67.8	78.8
	% time >7.8 mmol/L	51.7	51.6	43.3	39.5	30.7	20.7
	% time <3.5 mmol/L	2.0	1.5	1.1	1.6	1.5	0.5
	Mean glucose (mmol/L)	8.2	8.2	7.7	7.6	7.0	6.5
	HbA1c (mmol/mol / %)	53/7.0	54/7.1	54/7.1	53/7.0	52/6.9	
13	**% time in target (3.5-7.8 mmol/L)**	74.3	67.7	69.9	63.3	79.4	72.4
	% time >7.8 mmol/L	23.3	29.0	27.6	34.4	17.9	25.5
	% time <3.5 mmol/L	2.5	3.3	2.5	2.2	2.7	2.1
	Mean glucose (mmol/L)	6.6	6.8	6.8	7.4	6.3	6.8
	HbA1c (mmol/mol / %)	45/6.3	47/6.5	47/6.5	49/6.6	48/6.5	
14[*]	**% time in target (3.5-7.8 mmol/L)**	77.4	78.7				
	% time >7.8 mmol/L	21.1	18.3				
	% time <3.5 mmol/L	1.6	3.1				
	Mean glucose (mmol/L)	6.4	6.2				
	HbA1c (mmol/mol / %)	38/5.6	40/5.8	34/5.3	36/5.4	35/5.4	
15[‡]	**% time in target (3.5-7.8 mmol/L)**	41.6	70.6	73.2	68.7	56.8	
	% time >7.8 mmol/L	56.9	28.3	25.9	29.6	42.0	
	% time <3.5 mmol/L	1.5	1.1	0.9	1.7	1.2	
	Mean glucose (mmol/L)	8.6	6.9	6.8	7.0	7.8	
	HbA1c (mmol/mol / %)	53/7.0	47/6.5	48/6.5	51/6.8		
16	**% time in target (3.5-7.8 mmol/L)**	56.8	75.3	76.5	80.3	82.4	83.6
	% time >7.8 mmol/L	41.8	22.8	22.2	18.7	17.4	16.4

% time <3.5 mmol/L	1.3	1.9	1.3	1.0	0.2	0.1
Mean glucose (mmol/L)	7.6	6.5	6.6	6.5	6.5	6.4
HbA1c (mmol/mol / %)	45/6.3	45/6.3	47/6.5		46/6.4	

During the crossover study closed-loop use was overnight only. During the follow up phase closed-loop use was throughout the day and night.

*Participants 5 and 14 used sensor-augmented pump therapy without closed-loop after the crossover phase.

† Participants 4, 5, 6, 8, 10, and 11 were pump-naïve prior to enrolment in the study.

‡Participants 9 and 15 had used CGM prior to the study. All other participants were CGM-naïve.

2.4.5 Closed-loop during labour and delivery

Fourteen women continued closed-loop during labour and delivery (see Figure 2.4). In the 24 hours before delivery, participants using closed-loop had a median (interquartile range) glucose of 6.1 (5.8, 7.1) mmol/L, spent 86.8 (59.6, 94.1)% time-in- target (3.5-7.8 mmol/L) and 0.5 (0, 1.8)% time below 3.5 mmol/L. In the first 48 hours post-partum, participants had a median (interquartile range) glucose of 6.5 (5.8, 7.6) mmol/L, spent 73.7 (61.4, 86.0)% time-in-target and 0 (0, 0.5)% time below 3.5 mmol/L. Total daily insulin doses were 53.6 (48.6, 73.6)% of the pre-delivery dose; median (interquartile range) with substantial inter-individual variability (Table 2.9). There were no episodes of maternal hypoglycaemia during the 24 hours prior to delivery or 48 hours post-delivery.

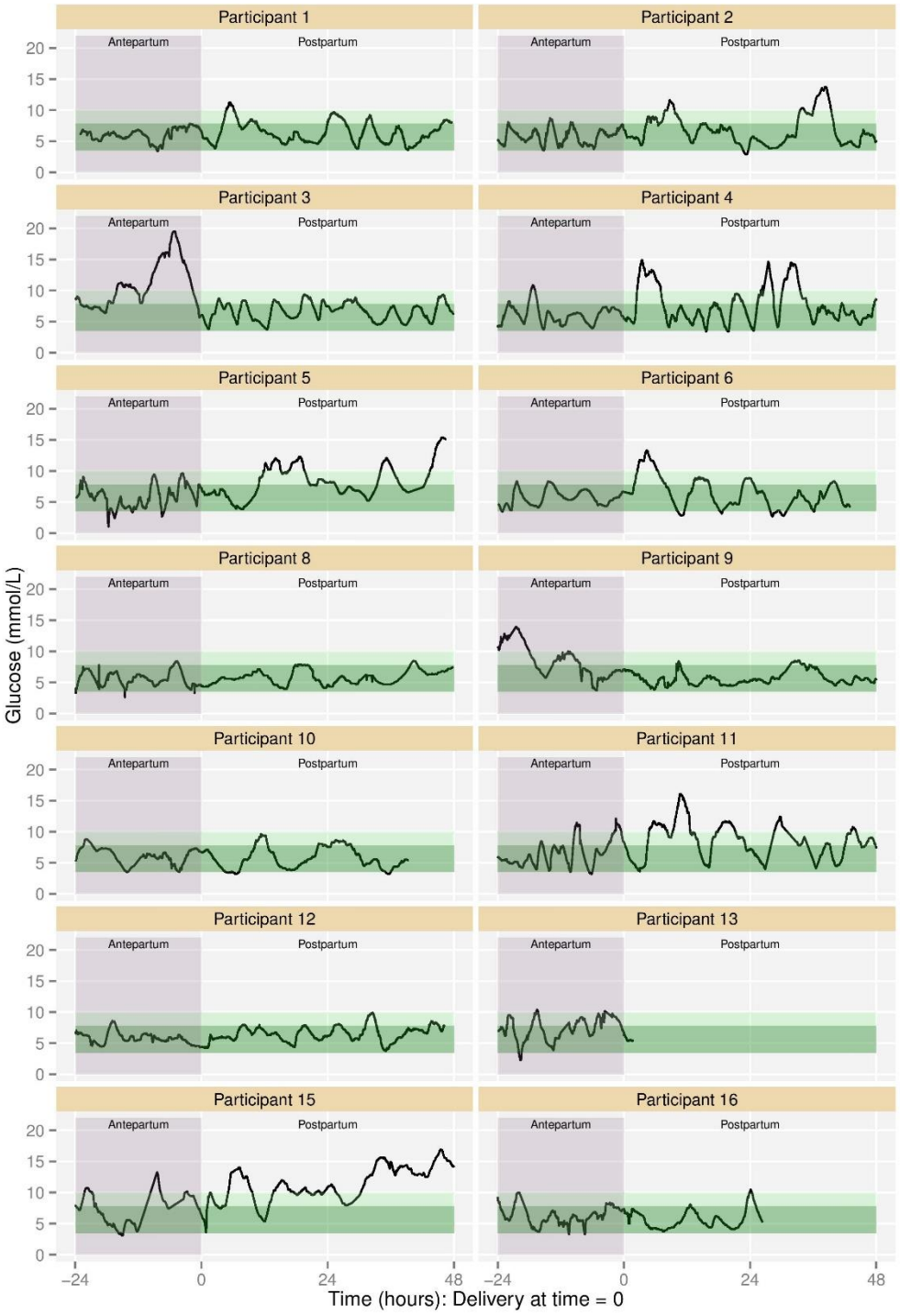


Figure 2.4: Individual graphs of glycaemic control by direct CGM measures during labour and delivery

Table 2.9: Total daily doses of insulin in the 24 hours prior to delivery and the first two days post-partum for participants using the closed-loop system

Participant number	Total insulin dose 24 hours prior to delivery (units)	Total insulin dose day 1 post-partum Units (% of pre-delivery dose)	Total insulin dose for day 2 post-partum Units (% of pre-delivery dose)
1	99.1	50.3 (50.8)	55.2 (55.7)
2	45.2	33.3 (73.5)	23.8 (52.5)
3	141.5	70.1 (49.5)	70.6 (49.9)
4	84.3	55.3 (65.6)	39.5 (46.9)
5	91.2	48.9 (53.6)	66.7 (73.1)
6*	51.2	79.5 (155.2)	27.4 (53.5)
8	No insulin data available		
9	101.3	31.0 (30.6)	30.8 (30.4)
10	39.4	19.2 (48.6)	23.6 (59.9)
11	150.9	124.4 (82.5)	84.5 (56.0)
12	48.8	29.3 (60.0)	37.3 (76.4)
13	65.0	Participant did not wear closed-loop for the 48 hours following delivery	
15‡	38.4	47.2 (123.0)	54.7 (142.5)
16	54.5	21.0 (38.6)	17.5 (32.2)

*Participant 6 had a high total daily insulin dose on day 1 post-partum as a result of high carbohydrate intake and accompanying large prandial boluses. On day 2 post-partum she resumed her normal dietary intake.

‡Participant 15 has co-existing primary adrenal insufficiency (Addison's disease) and was treated with 180mg IV hydrocortisone per day for 48 hours post-partum. When her data are excluded the median % of pre-delivery insulin dose on day 1 post-partum is 53.6 (48.6, 73.5) and on day 2 post-partum 53.5 (46.9, 59.9).

2.4.6 Obstetric and neonatal outcomes

Median (interquartile range) gestation at delivery was 36.9 weeks (34.5, 37.7 weeks). Five participants developed pre-eclampsia, including one with haemolysis, elevated liver enzyme and low platelets (HELLP) syndrome. Fifteen women delivered via caesarean section (two under general anaesthesia), ten of which were performed prior to onset of labour. One participant had an ovarian cystectomy during caesarean section. Seven participants delivered prior to 37 weeks gestation (four prior to 34 weeks) and six had antenatal glucocorticoids administered for fetal lung maturation. Participants spent a median of 58.1, 59.1, and 70.9% time-in- target (3.5-7.8 mmol/L) on days 1, 2, and 3 post-glucocorticoid administration. Closed-loop delivered a median of 169-178% of the pre-glucocorticoid insulin dose although there was substantial inter-individual variability (Tables 2.10-2.12). The median (interquartile range) birthweight was 3587.5 g (2670, 3997.5g). Thirteen of the 16 infants had a sex and gestational age-corrected birthweight above the 90th centile using a population-based UK reference (225). Twelve infants were admitted to neonatal intensive care, 11 of whom were treated with intravenous dextrose for neonatal hypoglycaemia. Details of individual obstetric outcomes are included in the Table 2.13.

Table 2.10: Glucose control (mean glucose and percentage time in target 3.5-7.8 mmol/L) and insulin doses after antenatal steroids; median (interquartile range)

	Average over 7 days prior to steroid administration	**0-24 hours post 1st steroid dose**	**24-48 hours post 1st steroid dose**	**48-72 hours post 1st steroid dose**
Time in target; %	73.0 (69.6, 79.4)	58.1 (48.3, 66.9)	59.1 (53.8, 70.8)	70.9 (66.0, 77.1)
Time >7.8 mmol/L; %	25.0 (20.2, 28.4)	41.8 (29.8, 51.6)	40.9 (24.4, 46.2)	26.5 (20.8, 32.6)
Time <3.5 mmol/L; %	2.1 (1.7, 2.3)	0.0 (0, 0.2)	0 (0, 0)	0.5 (0, 2.1)
Mean glucose; mmol/L	6.8 (6.4, 6.9)	7.5 (6.8, 8.1)	7.8 (7.2, 7.9)	6.7 (6.1, 7.3)
Total daily dose of insulin; units	40.7 (36.1, 59.8)	65.3 (60.0, 75.3)	70.1 (66.8, 83.1)	78.9 (60.1, 96.8)
Percentage of pre-steroid total daily dose of insulin; %	100	169 (111, 234)	176 (155, 224)	178 (103, 248)

Table 2.11: Glucose control (mean glucose and percentage time in target 3.5-7.8 mmol/L) prior to and in the first 72 hours after antenatal steroid administration by participant

Participant number	Measure	7 days prior to steroid administration	0-24 hours post 1st steroid dose	24-48 hours post 1st steroid dose	48-72 hours post 1st steroid dose
05	**Time in target %**	85.8	68.7	70.8	74.7
	Mean glucose; mmol/L	6.1	6.5	6.4	6.1
06	**Time in target %**	70.0	36.4	53.8	77.9
	Mean glucose; mmol/L	6.9	8.4	7.9	6.4
07	**Time in target %**	80.6	85.3	76.1	92.6
	Mean glucose; mmol/L	6.6	6.7	7.2	5.9
08‡	**Time in target %**	69.5	46.2	Closed-loop not operational	67.2
	Mean glucose; mmol/L	7.0	8.2		7.0
09	**Time in target %**	76.0	61.6	59.1	56.6
	Mean glucose; mmol/L	6.4	7.0	7.8	8.1
15	**Time in target %**	65.0	54.5	16.4	65.6
	Mean glucose; mmol/L	7.0	8.0	10.3	7.4

‡Overnight midwifery and obstetric staff were unfamiliar with the closed-loop system and set up a variable rate intravenous insulin infusion which was discontinued and replaced by closed-loop the following morning.

Table 2.12: Insulin doses prior to and in the first 72 hours after antenatal steroid administration by participant

Participant number	Average over 7 days prior to steroid administration; units	0-24 hours post 1st steroid dose; units (% of pre-steroid dose)	24-48 hours post 1st steroid dose; units (% of pre-steroid dose)	48-72 hours post 1st steroid dose; units (% of pre-steroid dose)
05	34.6	78.0 (226%)	61.0 (176%)	95.6 (277%)
06	61.9	146.4 (237%)	138.8 (224%)	108.2 (175%)
07	75.5	67.2 (89%)	66.8 (88%)	59.4 (79%)
08‡	40.7	46.1 (113%)	Closed-loop not operational	28.7 (70%)
09	53.4	58.9 (110%)	83.1 (155%)	97.2 (182%)
15	23.0	63.5 (276%)	70.1 (305%)	62.2 (270%)

‡Overnight midwifery and obstetric staff were unfamiliar with the closed-loop system and set up a variable rate intravenous insulin infusion which was discontinued and replaced by closed-loop the following morning

Table 2.13: Individual obstetric and neonatal outcomes with details of previous obstetric and medical complications

Participant number	Gravidity	Parity	Obstetric history	Medical history	Gestation at delivery	Antenatal steroids	Mode of delivery	Birthweight of infant (g)	Neonatal hypoglycaemia	Neonatal intensive care unit	Obstetric complications
1	4	2	1 miscarriage, 2 live births	N/A	37+0	No	C-section	3700	Yes, treated nasogastric feeds	No	N/A
2	1	0	N/A	N/A	38+4	No	C-section	3455	No	No	N/A
3	5	3	1 stillbirth, 1 miscarriage, 2 preterm live births <34 weeks	Hypertension	34+5	No	C-section*	2700	Yes, treated IV dextrose	Yes	Intrapartum UTI
4	3	1	1 termination malformation, 1 live birth	N/A	37+1	No	NVD (IOL)	4020	Yes, treated supplemental feeds	No	2nd degree tear
5	3	2	2 preterm live births <34/40	N/A	31+1	Yes	C-section*±	1382	Yes, treated IV dextrose	Yes	Premature rupture of membranes, post-partum haemorrhage
6	1	0	N/A	N/A	37+2	Yes	C-section	3515	No	Yes	N/A
7	1	0	N/A	N/A	35+1	Yes	C-section*	2870	Yes, treated IV dextrose	Yes	Preeclampsia & HELLP syndrome.
8	2	0	1 miscarriage	N/A	33+6	Yes	C-section*	2520	Yes, treated IV dextrose & nasogastric feeds	Yes	Preeclampsia

9	3	1	1 stillbirth, 1 miscarriage	Rheumatoid arthritis, Coeliac disease, Hypertension, Factor V leiden thrombophilia	28+4	Yes	C-section*	850	Yes, treated IV dextrose	Yes	Preeclampsia
10	1	0	N/A	N/A	38+2	No	C-section*	4155	Yes, treated IV dextrose	Yes	Post-partum haemorrhage
11	2	0	1 miscarriage	N/A	37+5	No	C-section*	4530	Yes, treated IV dextrose	Yes	N/A
12	1	0	N/A	N/A	37+5	No	C-section*	4632	Yes, treated supplemental feeds	No	Preeclampsia
13	2	1	1 livebirth	N/A	37+2	No	C-section	3825	Yes, treated IV dextrose	Yes	N/A
14	1	0	N/A	Hypertension	38+5	No	C-section	3990	Yes, treated IV dextrose	Yes	Exacerbation of pre-existing hypertension
15	1	0	N/A	4x islet cell transplants, Addison's, hypothyroid	33+5	Yes	C-section*	2580	Yes, treated IV dextrose	Yes	Preeclampsia
16	3	2	2 livebirths	N/A	36+5	No	C-section*+	3660	Yes, treated IV dextrose	Yes	Placenta praevia

*Caesarean section before onset of labour. The five remaining participants experienced caesarean section after the onset of labour.
*±Caesarean section under spinal anaesthesia followed by ovarian cystectomy under general anaesthesia.
+Caesarean section under general anaesthesia.
Participants 11 and 12 had euglycaemic c-peptide results of 64 and 119 pmol/L respectively.

2.5 Discussion

Compared with sensor-augmented pump therapy, overnight closed-loop resulted in a significant (15% percentage point) increase in the time spent within the glucose target range for pregnancy. These improvements were achieved without an increased incidence of hypoglycaemia or an increase in total insulin dose, but with more variable insulin delivery targeted to minimise hyperglycaemic excursions. The improved glycaemic control associated with overnight closed-loop system resulted in a lower mean glucose and higher percentage of time with target glucose over 24 hours.

Fourteen participants continued day-and-night closed-loop for up to an additional 14 weeks, demonstrating the feasibility of 24-hour use of closed-loop during pregnancy and in the immediate 48 hours post-partum. This is important because pregnancy poses challenges to the use of a closed-loop system, some of which are integral to pregnancy (e.g., week-by-week changes in insulin resistance and pharmacokinetics (13), labour and delivery, and the rapid decrease in insulin requirements post-partum). Further challenges arise from acute antenatal admissions, administration of corticosteroids for fetal lung maturation, and the use of anaesthesia for caesarean section. Previous outpatient studies (191,192) have focused on relatively steady-state diabetes outside of pregnancy. Here we demonstrate that the built-in adaptability of the closed-loop system could safely maintain maternal glycaemic control throughout pregnancy, delivery, and in the immediate post-partum period without any announcement of these events to the system, and without any severe hypoglycaemia requiring assistance. Notably, 15 of the 16 women in this trial delivered via caesarean section (although 5 of these were after the onset of labour) and so the generalisability of our results during labour and delivery must be considered in that context. Further the lack of control group during the follow up phase means that the performance of this system compared with existing treatments during antenatal steroid use and other pregnancy challenges is not possible from our results.

The randomised crossover design reduced the impact of confounding factors. There was no significant effect of period or gestational age, suggesting that closed-loop adjusted

insulin consistently. No prior closed-loop studies have included participants using multiple daily insulin injections. We included 14 sensor naïve and six pump naïve participants. We found that their glycaemic control outcomes were comparable to experienced users, although the study was not designed to formally compare these different groups of participants.

Our findings build on recent trials demonstrating that a closed-loop system resulted in improved glycaemic control, without increased hypoglycaemia or insulin dose, as compared with sensor-augmented pump therapy (191,192). The glucose control achieved during our *control* phase is comparable to that achieved by artificial pancreas interventions in non-pregnant participants, reflecting the unique motivation of pregnant women and tighter glycaemic targets. Despite impressive glycaemic control with sensor-augmented pump therapy, closed-loop still generated substantial improvements when used overnight.

This study was conducted in an extremely high risk cohort. Our sample size was small but included women with long duration of diabetes and substantial prior obstetric morbidity including spontaneous pregnancy losses, one second trimester termination, two early preterm deliveries and two stillbirths. This perhaps contributes to the unexpectedly high rates of pre-eclampsia, large-for-gestational-age, and neonatal hypoglycaemia given the good glycaemic control achieved. Fetal hyperinsulinaemia and increased placental fuel transfer can persist with apparently normal maternal glycaemia and may in part explain these outcomes. The higher than expected rates of maternal and infant complications may be in part due to chance given our small sample size and high risk cohort. However, others have also found high rates of macrosomia and neonatal hypoglycaemia in women who have good glycaemic control (124) and this raises the question about whether our glucose-centric approach is limited, and these complications may relate to factors beyond glucose control alone.

Larger trials of longer duration closed–loop therapy are needed to evaluate obstetric and neonatal outcomes. Additionally, while the system was relatively easily introduced into the centres in which this trial was conducted and was well-received by midwifery, obstetric, diabetology, and anaesthetics colleagues, it should be noted that significant

support was provided by the research team to ensure a smooth introduction of the technology. Future research should take into account staff perceptions outside of major research centres and ensure that all staff are adequately equipped to oversee treatment of women using closed-loop systems in their centres.

2.6 Conclusion

In conclusion, we found that overnight closed-loop resulted in improved glucose control in pregnant women with type 1 diabetes in pregnancy when compared to sensor-augmented pump therapy. In the continuation phase, day-and-night closed-loop maintained glycaemic control for a high proportion of the time during antenatal hospital admissions, labour and delivery, suggesting that longer-term clinical efficacy trials are warranted.

3. Day-and-night closed-loop in pregnancy

3.1 Background

Type 1 diabetes in pregnancy is associated with increased risk of maternal and neonatal complications (1,49,56,58,69). These complications occur more commonly in women with poorer glycaemic control, which is attributed to greater fetal exposure to maternal hyperglycaemia (226,227). Thus, the primary focus of treatment of type 1 diabetes in pregnancy is to reduce fetal exposure to hyperglycaemia without increasing maternal hypoglycaemia. Recent evidence suggests that continuous glucose monitoring (CGM) improves day-to-day glucose control, with approximately one hour per day less hyperglycaemia in women using multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) (150).

However, even with targeted efforts to improve glycaemic control before and during pregnancy, and with increasing use of CSII and CGM, pregnant women with type 1 diabetes continue to spend an average of eight hours each day hyperglycaemic (glucose concentration >7.8 mmol/L) (8,150). Furthermore, half of all infants born to women with type 1 diabetes have complications related to maternal hyperglycaemia, such as preterm delivery and large-for-gestational-age, which contribute to high rates of neonatal intensive care unit (NICU) admissions (36,150,227).

Closed-loop systems are automated insulin delivery systems that are designed to more closely mimic a healthy pancreas and enable tighter glucose control than what is achievable using currently available diabetes treatments. Hybrid closed-loop insulin delivery provides automated glucose-responsive insulin delivery between meals and overnight, with manually triggered pre-meal boluses (187). Closed-loop systems have been evaluated in children, adolescent, and adult populations under inpatient, outpatient, and home conditions and are associated with reduced exposure to hyperglycaemia and hypoglycaemia without increased insulin doses (173,191,222). Short term studies including non-pregnant adults with near-optimal glucose control (HbA1c <7.5%) suggest potential for reduced hypoglycaemia compared to conventional therapy (186). A recent systematic review and meta-analysis including 585 participants across 27 outpatient studies found consistent improvements in glucose control across a wide variety of clinical settings and closed-loop systems (228).

Closed-loop systems may be particularly useful in pregnancy, when glucose targets are tighter and hypoglycaemia burden is increased (9). The physiological changes in insulin sensitivity make day-to-day glucose control challenging throughout pregnancy (6). Pregnancy is also typically associated with heightened emotional intensity owing to women's awareness of the impact hyperglycaemia on fetal growth and development (77,78).

In Chapter 2, I presented the first home trial of a closed-loop system in pregnant women during the overnight period. The system was associated with a 15% increase in time spent with target blood glucose concentration during the overnight period (23.00-0700hrs) compared with sensor-augmented pump therapy. However, achieving and maintaining optimal glucose control is more challenging during the daytime when meal and exercise required precise insulin dose adjustments and the routine is more varied than during the overnight period (14). It is demanding for the majority of women with type 1 diabetes during pregnancy, 85% of whom enter pregnancy with higher-than-recommended HbA1c levels (227).

3.2 Aim

To determine the feasibility, utility, safety, and efficacy of automated day-and-night closed-loop insulin delivery in the home setting in the short term.

3.3 Methods

3.3.1 Study design

The trial was an open-label, randomised, two-period cross-over study in pregnant women with T1DM, assessing the feasibility, utility, safety and efficacy of day and night automated closed-loop insulin delivery, as compared to the use of sensor-augmented pump therapy, in the home setting.

After providing written informed consent, participants were trained in the use of the study CGM (FreeStyle Navigator 2, Abbott Diabetes Care, Alameda, CA, USA) and pump (DANA-R, Diabecare, SOOIL, Seoul, South Korea) devices and practiced using them for a two to four week period, after which time a careful assessment of subjects' competency in the management of the devices was carried out.

Using permuted four-block randomisation, participants were then randomised to either four weeks of closed-loop insulin delivery (intervention) or four weeks of real-time CGM and CSII without closed loop insulin delivery (sensor-augmented pump therapy; control). During the control phase, the sensor-augmented pump therapy did not have a low glucose suspend feature. At the end of the first study phase there was a one to two week washout period, before participants crossed over to the alternate phase. Women participated in the study from within the home setting, with 24-hour support available from the Cambridge clinical research team throughout the intervention and washout periods.

At the end of the randomised crossover trial, women could choose to resume their previous intensive insulin therapy or to continue to use the study devices (any combination of CGM, pump, or closed-loop) throughout the remainder of their pregnancy and delivery and for up to 6 weeks post-partum. This allowed for longer-term feasibility assessment and minimized ethical concerns about discontinuing a potentially beneficial treatment during pregnancy (229). The clinical research team provided all study participants and their clinical care teams with advice and support until 6 weeks after delivery. Details of the flow or participants through the trial are shown in Figure 3.1.

The randomisation schedule was created with an automated web-based programme, using a permuted four-block schedule maintained in a secure database, ensuring that allocation was concealed from trial staff and participants. Participants and staff were not masked to treatment allocation.

Finger-stick capillary blood glucose testing was recommended at least seven times daily with standard glucose targets in both groups (pre-meal 3.5-5.5 mmol/L, one hour post-meal <7.8 mmol/L). There were no restrictions on physical activity, meals or overseas travel and no remote monitoring. Participants had antenatal clinic visits every two weeks with fetal ultrasound assessments at 20, 28, 32, and 36 weeks' gestation or as clinically indicated.

HbA1c measurements were taken at baseline, the end of each crossover period, at 28, 32, and 36 weeks' gestation, and at six weeks after delivery. They were analysed at a central laboratory (Addenbrooke's Hospital, Cambridge, England) using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aligned method (TOSOH Bioscience G7 HPLC analyser; inter-assay CV 3.71% at HbA1c 5.41%; 1.7% at HbA1c 10.6%).

Quality, duration and fragmentation of sleep were assessed subjectively using the Pittsburgh Sleep Quality Index (PSQI; Appendix A) and a daily sleep diary (Appendix B), and objectively by actigraphy (Actiwatch 2, Philips Respironics) (230). These measures were conducted over 7 days at baseline, and then for days 21 to 28 of both intervention arms. Actigraphy data were downloaded from the Actiwatch 2 to Actiware computer software (Version 6.02).

The PSQI is a validated 19-item questionnaire that holistically assesses sleep quality and sleep duration over the preceding month (230). The sleep diary recorded time of going to bed and waking, plus time of, and reason for any nocturnal awakenings (e.g., urination or infant feeding). The Actiwatch was worn on the non-dominant wrist to provide objective measures of sleep and wakefulness based on motor activity (actigraphy). Actiwatches use an accelerometer to measure body movement in order to record time in bed and actual sleep time, as well as changes in sleep quality from measures of sleep maintenance, sleep efficiency, sleep latency, fragmentation index, total nocturnal activity, and percentage moving time (231–233).

Participants completed questionnaires (the Diabetes Technology Questionnaire; Appendix C, and the Hypoglycaemia Fear Survey II; Appendix D) at baseline and at the end of each crossover period (234,235). Adverse events were captured throughout the trial. Reportable averse events included all serious adverse events other than pre-specific protocol exceptions. Maternal antenatal, delivery, and neonatal outcomes were documented.

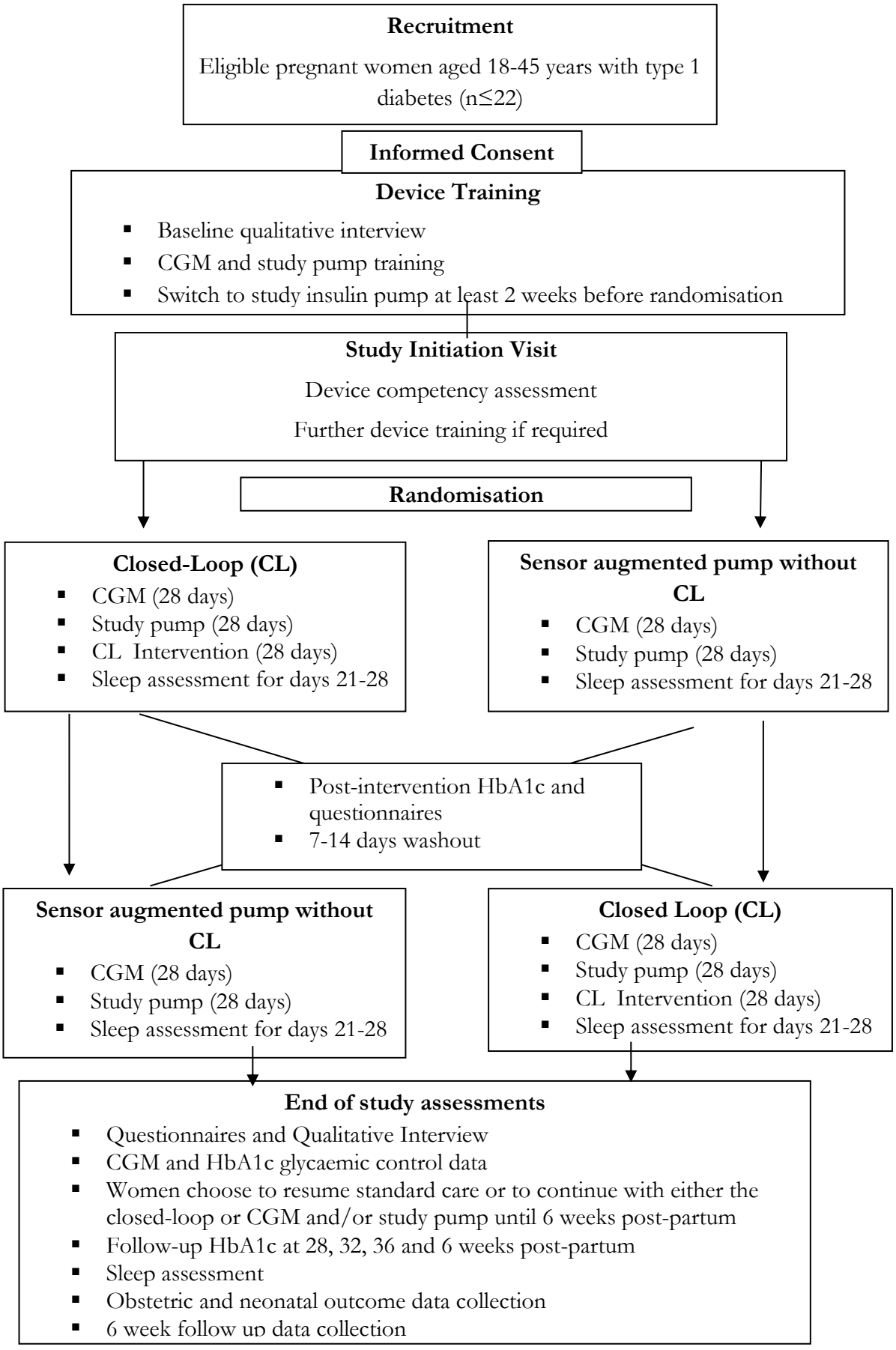


Figure 3.1: Diagram demonstrating flow of participants through trial

3.3.2 Study participants

We recruited pregnant women who had type 1 diabetes that was diagnosed at least 1 year prior to pregnancy. At recruitment, participants were aged between 18 and 45 years, had a singleton pregnancy confirmed on ultrasound and were between 8 and 24 weeks' gestation. They had had intensive insulin treatment for at least three months via either multiple daily injections (MDI) or insulin pump therapy, and a booking (first antenatal visit) HbA1c of 6.5-10%. Participants were required to understand and speak English and to have access to email.

The exclusion criteria were:

- Having non-type 1 diabetes mellitus
- Having a physical or psychological disease likely to interfere with the normal conduct of the study
- Taking medications known to significantly interfere with glucose metabolism
- Having a known or suspected allergy to insulin
- Having nephropathy, neuropathy, gastroparesis or proliferative retinopathy likely to interfere with the normal conduct of the study or interpretation of the results, as judged by the investigator
- Having a total daily insulin dose of ≥1.5 units per kilo at booking
- Having a first antenatal HbA1c ≤47 mmol/mol (<6.5%) or a current HbA1c ≥ 86 mmol/mol (10%)

3.3.3 Study oversight

The clinical study protocol was approved by the Health Research Authority, East of England Regional Ethics Committee (15/EE/0278), with notification of no objection provided by the Medicines and Healthcare Products Regulatory Agency, UK (CI/2015/0042).

All participants provided written informed consent. The trial was overseen by a Trial Steering Committee. Abbott Diabetes Care provided discounted continuous glucose monitoring devices and consumables. They played no role in study design nor the collection, handling, analysis, or interpretation of data.

3.3.4 Closed-loop system

The closed-loop system (Florence D2A, University of Cambridge, Cambridge, UK) used continuous CGM-derived glucose measurements in order to automatically adjust basal insulin rates. Real-time interstitial glucose readings were transmitted using Bluetooth via a purpose-built translator to an Android mobile phone (Samsung Galaxy S4, Samsung, South Korea), which housed the closed-loop algorithm that determined an appropriate insulin dose (Figure 3.2). The control algorithm (University of Cambridge, Version 0.3.41p) aimed for an interstitial glucose concentration of 5.8 to 7.3 mmol/L, adjusting for fasting and post-meal conditions and for accuracy of glucose prediction. It incorporated learning about day-to-day insulin doses and adapted insulin delivery for particular times of day when individual participant requirements were higher or lower. Every 12 minutes, the insulin dose was communicated via Bluetooth to the insulin pump, which then delivered the insulin. The study insulin pumps (DANA) were modified in-house (replacement caps inserted) to allow participants to select their preferred insulin infusion set.

Pre-meal insulin boluses were given manually 15 to 30 minutes before eating using the pump's inbuilt bolus calculator or an interface housed on the mobile phone. To initialise closed-loop, the participant's weight and total daily dose of insulin were manually entered into the algorithm and the participant's usual insulin pump settings were automatically transferred to the algorithm using Bluetooth. Safety rules limited maximum insulin dose and suspended insulin delivery when the glucose concentration was falling rapidly and/or <4.3 mmol/L. Capillary glucose calibration tests were advised twice daily (before breakfast and evening meal). Recalibration of CGM was recommended if the sensor and capillary glucose measurements differed by ≥3.0 mmol/L. During the four week randomised phase and subsequent periods of closed-

loop use, participants were instructed to use the system continuously. To maintain device connectivity, participants had to be within approximately 30 metres of the devices. There were no changes made to the system to announce or adjust for antenatal corticosteroid use, labour, or delivery.

At the start of the closed-loop study phase, participants had a device training session (30 to 60 minutes) at their antenatal clinic or at home. This included instructions for starting and stopping closed-loop operation and for troubleshooting basic technical issues. Participants had access to a 24-hour phone line staffed by the research team for technical issues they could not resolve with their training.

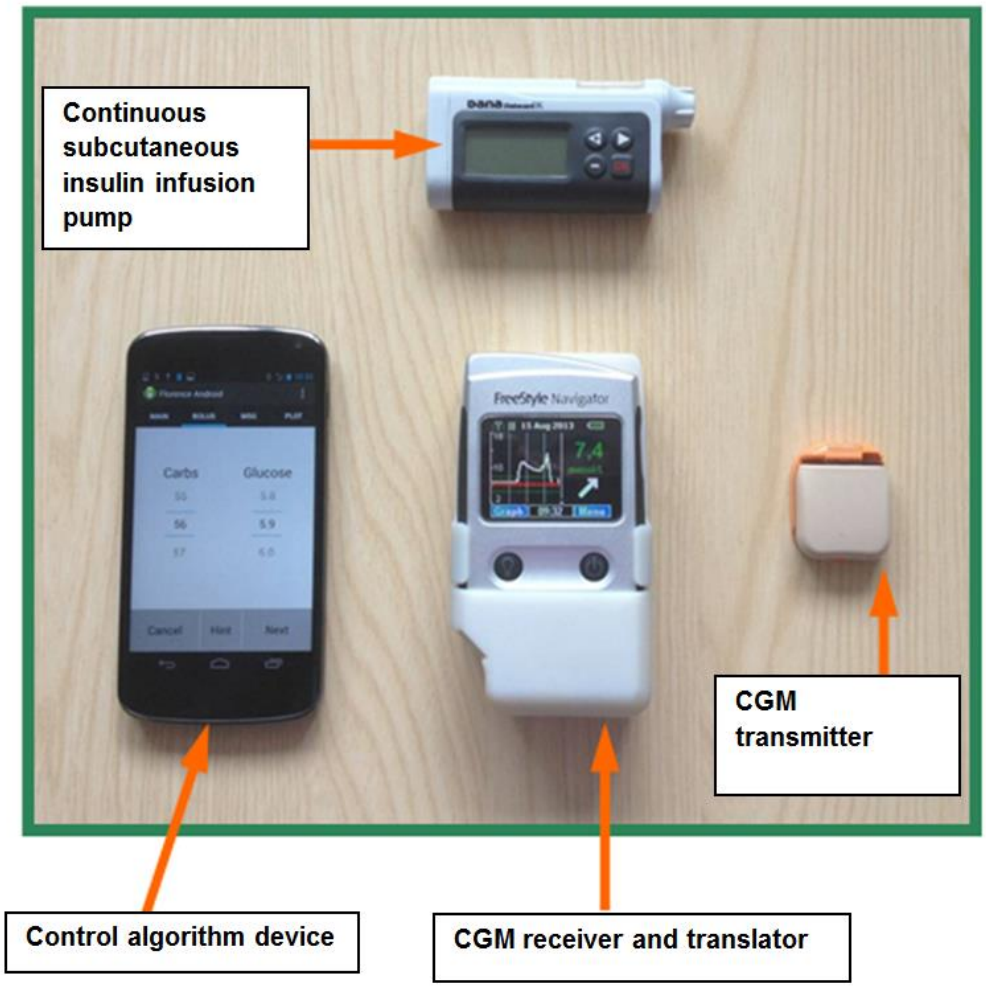


Figure 3.2: Components of the closed-loop system

3.3.5 Study endpoints

The primary efficacy endpoint was the percentage time spent within the target glucose range (3.5-7.8 mmol/L), as measured by CGM during the four-week intervention periods.

The secondary efficacy outcomes were:

- Percentage time spent with sensor glucose ≥3.5 and ≤7.8 mmol/L to quantify time spent in the recommended "normoglycaemic" target range during pregnancy
- Percentage time spent with sensor glucose <3.5 mmol/L to quantify borderline hypoglycaemia
- Percentage time spent with sensor glucose ≤2.8 mmol/L to quantify moderate hypoglycaemia
- Percentage time spent with sensor glucose >7.8 mmol/L to quantify the duration of hyperglycaemia
- Percentage time spent with sensor glucose >10.0 mmol/L to quantify significant hyperglycaemia
- Percentage time spent with sensor glucose >3.5 to ≤10.0 mmol/L to quantify near optimal target range
- Area under the curve (AUC) for sensor glucose >7.8 mmol/L, >6.7 mmol/L, <3.5 mmol/L, and <2.8 mmol/L
- Percentage time CGM worn to quantify compliance
- LBGI to quantify the risk of hypoglycaemia (236)
- Standard deviation of the rate of change of sensor glucose to quantify the glucose variability
- Insulin delivered (basal, bolus, and total) to assess insulin needs
- HbA1c and average sensor glucose to quantify glucose control
- Episodes of severe hypoglycaemia requiring assistance
- Mild-moderate episodes of hypoglycaemia <3.5 mmol/L (mild) and <2.8 mmol/L (moderate) for 20 minutes duration

- Nocturnal hypoglycaemia (NH): CGM glucose <3.5 (mild) and <2.8 (moderate) between 23:00 and 07:00 hours

Safety end points included the number and duration of hypoglycaemic episodes (moderate or severe). Moderate hypoglycaemia was defined as a glucose concentration of <3.5 mmol/L for 20 minutes or longer, as measured by continuous glucose monitoring. A severe hypoglycaemic episode was defined as an episode requiring third-party assistance.

The feasibility of day-and-night closed-loop therapy in the continuation phase (from the end of the crossover phase until delivery) was assessed on the basis of glucose measurements during sequential 4-week intervals and over the period as a whole. The same glucose targets and study end points were used during the crossover and continuation study phases, with the target range adjusted from 3.5-7.8 mmol/L to 3.9-10.0 mmol/L during the post-partum phase. While participants were generally instructed to aim for glucose levels between 6.0 and 10.0 mmol/L in the early post-partum phase, the non-pregnancy target range was used for statistical analysis in order to facilitate comparison with other published cohorts.

3.3.6 Statistical analysis

Previous study participants using sensor augmented pump therapy spent 61.7 (24.9) % time in the recommended glucose target range during pregnancy with type 1 diabetes (14). To detect a 30% relative increase (from 62% to 80% time-in-target range), we estimated that a sample size of 16 participants was needed to achieve 80% power and an alpha level of 0.05 (two-tailed). The standard deviation of the primary outcome was assumed to be 25% (13,14).

Statistical analyses were performed on an intention-to-treat basis and analysed according to the study phase to which the participant was allocated, regardless of compliance. A 5% significance level was used for all comparisons without adjustment for multiplicity. Outcomes were calculated with GStat Version 2.2 software (University of Cambridge, Cambridge UK) and statistical analyses performed using SPSS and R. Results during the randomised crossover study phases were compared using linear mixed effects models, with the response variable being time-in-target range; the study arm as a fixed effect; and study participant and four-week block within participant as nested random effects. The model's fit was not improved by including terms for either period by study arm interaction.

3.4 Results

3.4.1 Study participants

Nineteen participants were recruited to the study (Figure 3.3). Of these, two participants withdrew prior to randomisation (one disliked the study pump and one experienced a mental health deterioration) and one withdrew post-randomisation following the development of pregnancy complications. This participant had preterm premature rupture of membranes with severe oligohydramnios during her first study arm (sensor-augmented pump therapy) at 20 weeks gestation. She underwent a termination of pregnancy due to poor fetal prognosis, necessitating withdrawal from the study. Sixteen participants completed both study arms and are included in analyses. Their baseline characteristics are presented in Table 3.1. There were equal numbers of pump and MDI users and nine (56%) participants who entered pregnancy with HbA1c levels >7.5%.

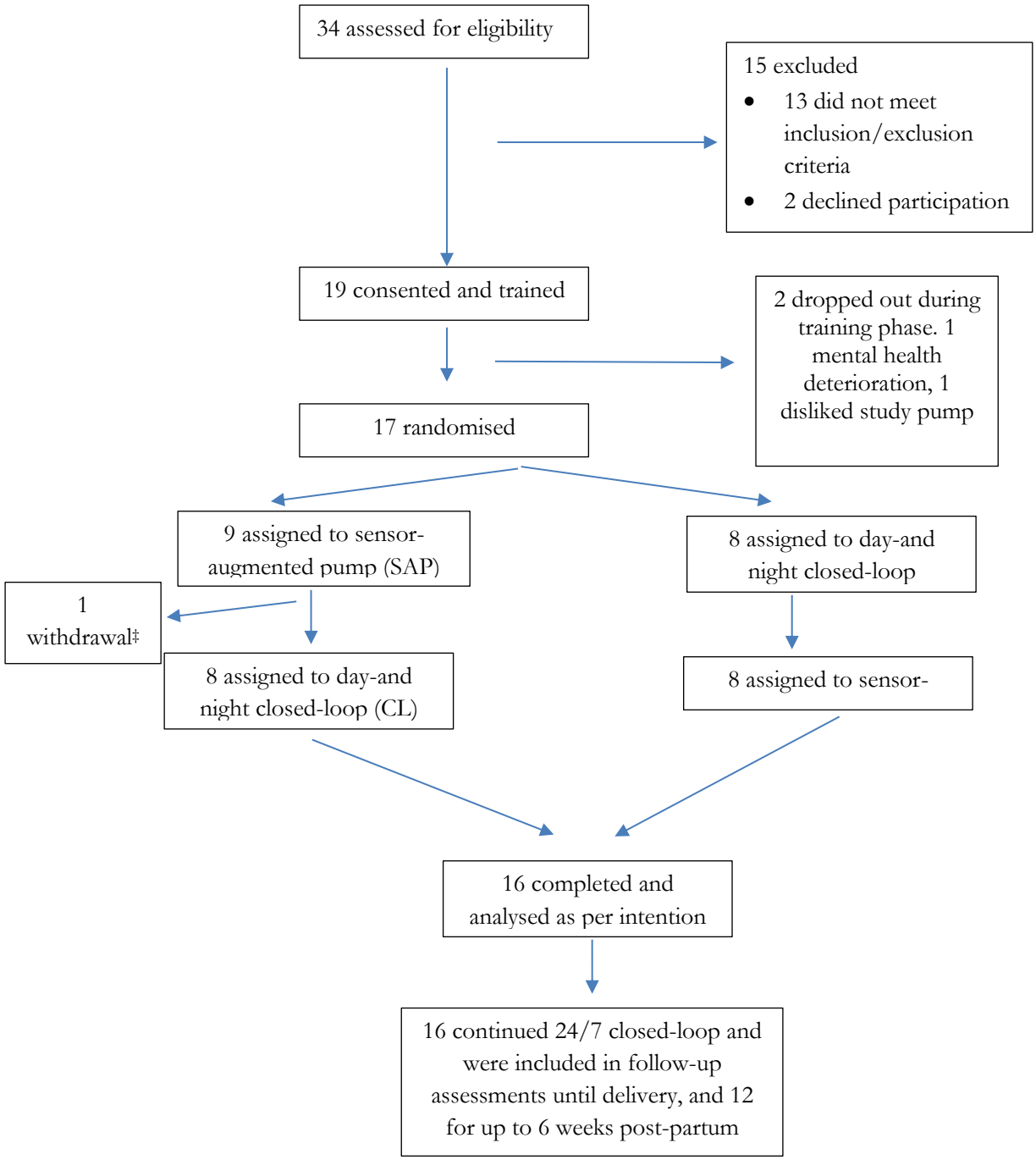


Figure 3.3: Consort diagram

‡Withdrawal due to preterm premature rupture of membranes, severe oligohydramnios and termination of pregnancy due to poor fetal prognosis

Table 3.1: Baseline characteristics

Baseline characteristics (N=16)	**Number (%)**	**Mean (SD)**
Age (years)		32.8 (5.0)
BMI (kg/m^2)		26.6 (4.4)
Booking HbA1c (%)		8.0 (1.1)
Booking HbA1c (mmol/mol)		63.7 (12.1)
Booking HbA1c >7.5% (58 mmol/mol)	9 (56%)	
Duration of diabetes (years)		19.4 (10.2)
Insulin pump use prior to study	8 (50)	
CGM use prior to study[±]	3 (19)	
Total daily insulin dose (units/kg/day)		0.51 (0.09)
Weeks gestation[*]		16.4 (4.9)
Primiparous[‡]	6 (38)	
Recruitment site		
Cambridge	6 (38)	
Norwich	8 (50)	
Ipswich	2 (12)	

[*]HbA1c and weeks gestation at randomisation. Randomisation was performed after recruitment and 2 to 4 weeks of device training when insulin regimens were optimised and participants were competent using the study devices.

[±]None of the 3 participants had used CGM in the 6 months prior to enrollment in the study or as part of their regular diabetes management. 2 participants had used real-time CGM, and one Freestyle Libre.

[‡]6 participants had experienced previous pregnancy losses (6 miscarriages and 1 stillbirth), 2 women had had second trimester termination of pregnancy for major malformation, and 2 women had a history of hypertensive disorders of pregnancy.

3.4.2 Study outcomes

There was no difference in the primary outcome, percentage of time spent with target glucose concentration (3.5-7.8 mmol/L) during closed-loop and sensor-augmented pump therapy (62.3% vs 60.1%; absolute difference 2.1%, $CI_{95\%}$ -4.1 to 8.3; $p = 0.47$, Table 3.2). Likewise, the mean CGM glucose and time spent above target (7.8 mmol/L) did not differ between closed-loop and sensor-augmented pump therapy (7.3 vs 7.3 mmol/L; $p = 0.85$ and 36.6 vs 36.1%; $p = 0.86$). During the four-week closed-loop phase, there were fewer episodes of maternal hypoglycaemia (median [range] 8 [1-17] vs 12.5 [1-53]; $p = 0.04$), and less time below 3.5 mmol/L (1.6 vs 2.7%; $CI_{95\%}$ -0.2 to 2.1; $p = 0.02$). Time below 2.8 mmol/L (0.24 vs 0.47%; $CI_{95\%}$ -0.02 to -0.5; $p = 0.03$) and low blood glucose index (LBGI; 1.0 vs 1.4; $CI_{95\%}$ -0.7 to -0.1; $p = 0.01$) were lower during closed-loop, as was overnight time (2300-0700 hrs) below 3.5 mmol/L (1.1 vs 2.7&; $CI_{95\%}$ -2.8 to -0.4; $p = 0.008$). There were no episodes of severe hypoglycaemia during either study phase. Overnight time-in-target was 7.2% higher during closed-loop therapy than during sensor-augmented pump therapy, but this difference did not reach statistical significance (Table 3.3). There were no differences in glycaemic control between participants who had or had not used pump therapy prior to the study (Table 3.5).

Continuous glucose monitoring was active for an average of 20.3 hours per day during sensor-augmented pump therapy and 20.2 hours per day during closed-loop study arm ($p = 0.92$). However, there was substantial inter-participant variability, with average wear ranging from 10.0 to 23.4 hours per day during sensor-augmented pump therapy and 13.4 to 23.4 hours per day during the closed-loop study arm.

Table 3.2: Comparison of sensor-augmented pump therapy and closed-loop automated insulin delivery during the crossover phase of the study. Pre-meal boluses were given manually (15 to 30 minutes before eating). The values reported are derived from linear mixed effects models.

	Sensor-augmented pump	**Closed-loop**	**Absolute difference ($CI_{95\%}$)**	**P value**
Crossover phase				
Time in target[*] (3.5-7.8 mmol/L) (%)	60.1	62.3	2.1 (-4.1 to 8.3)	0.47
Time above target (%)	36.6	36.1	-0.6 (-7.4 to 6.3)	0.86
Time with glucose above 10 mmol/L (%)	14.8	14.6	-0.1 (-4.2 to 4.0).	0.94
Time below target (%)	2.7	1.6	-1.1 (-0.2 to -2.1)	0.02
Time with glucose below 2.8 mmol/L (%)	0.47	0.24	-0.2 (-0.02 to -0.5)	0.03
Number of hypoglycaemic events (Median [range]; <3.5 mmol/L for ≥20 minutes)	12.5 (1-53)	8 (1-17)		0.04
Low blood glucose index[±]	1.4	1.0	-0.4 (-0.7 to -0.1)	0.01
Mean glucose (mmol/L)	7.3	7.3	0 (-0.3 to 0.4)	0.85
Standard deviation of sensor glucose (mmol/L)	2.1	2.0	-0.7 (-0.2 to 0.1)	0.29
TDD insulin (units/day)	43.7	41.5	2.2 (-6.4 to 0.7)	0.56
Sensor wear (hours)	20.3	20.2		

[*] The primary efficacy endpoint was the percentage of time that glucose was in the target range of 3.5-7.8 mmol/L overnight, as recorded by CGM during each four week study phase. The percentage time above target refers to the time that the glucose concentration was above 7.8 mmol/L and percentage time below target as the time that the glucose concentration was lower than 3.5 mmol/L.

[±]The low blood glucose index assessed the duration and extent of hypoglycaemia.

Table 3.3: Overnight (2300-0700hrs) glucose control during the randomised crossover study

	Sensor-augmented pump	Closed-loop	Absolute difference ($CI_{95\%}$)	*p*-value
Overnight glycaemic control during crossover phase				
Time in target (3.5-7.8 mmol/L) (%)	60.6	67.7	-7.2 (-0.8 to 15.2)	0.06
Time above 7.8 mmol/L (%)	36.7	31.1	-5.5 (-14.0 to 2.9)	0.18
Time above 10 mmol/L (%)	14.1	11.7	-2.4 (-7.0 to 2.3)	0.29
Time below 3.5 mmol/L (%)	2.7	1.1	-1.6 (-2.8 to -0.4)	0.008
Time below 2.8 mmol/L (%)	0.5	0.2	-0.3 (-0.6 to 0.0)	0.06
Mean glucose (mmol/L)	7.2	7.2	-0.04 (-0.5 to 0.4)	0.83

Table 3.4: Insulin doses during the randomised crossover study

	Sensor-augmented pump therapy	Closed-loop	*p*-value
Total daily dose (units/day)	43.7	41.5	0.56
Basal (units/day)	16.8 (38.5%)	21.2 (51.1%)	0.73
Bolus (units/day)*	26.9 (61.5%)	20.3 (48.9%)	0.83
Standard deviation of basal insulin (units)	0.1	0.8	<0.0001

*During closed-loop pre-meal boluses were given manually (15-30 minutes before eating) using the pump's inbuilt bolus calculator via an interface housed on the mobile phone. During the sensor- augmented pump control phase pre-meal boluses were given manually (15 to 30 minutes before eating) using the pump's inbuilt bolus calculator.

Table 3.5: Glycaemic control during the randomised crossover study and follow up phase in participants who were using multiple daily injections (MDI) vs insulin pump therapy at enrolment

	Previous MDI users (n=8)						**Previous Pump users (n=8)**					
	Sensor-augmented pump	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**	**Sensor-augmented pump**	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**
% Time in target (3.5-7.8 mmol/L)	57.3	58.4	1.1	71.7	70.5	71.7	62.4	66.4	4.0	71.7	73.3	78.2
% Time below 3.5 mmol/L	0	0.25	0.25	3.7	3.0	1	0.6	0.1	-0.5	1.7	1.4	2.8
Mean glucose (mmol/L)	7.5	7.7	0.2	7.1	6.8	7.1	7.3	7.1	-0.2	6.9	6.7	6.6

There were no significant differences between previous MDI vs pump users in either study arm of the crossover phase or at any point in the follow up phase (p >0.05 at all time points).

The mean (SD) HbA1c was 48.5 (7.5), 45.9 (5.5), and 46.3 (5.6) mmol/mol at baseline, end of the sensor-augmented pump therapy arm, and end of the closed-loop arm, respectively. There was no difference in HbAc between baseline and either the end of the sensor-augmented pump therapy or the closed-loop therapy arms (p = 0.15 and p = 0.14 respectively), and no difference in HbA1C between the two study arms (p= 0.67). There were no differences in average total insulin doses between the closed-loop and sensor-augmented pump therapy phases, although, as expected, insulin delivery was significantly more variable during closed-loop use.

3.4.3 Quality of sleep during crossover study

The quality and quantity of sleep were comparable during closed-loop and sensor-augmented pump therapy, with a mean (SD) sleep duration of 7.5 (0.8) and 7.1 (1.2) hours, p = 0.22 (Table 3.6). The mean sleep efficiency also did not differ between closed-loop and sensor-augmented pump therapy (84.2 (3.8) vs 80.5 (7.9)%, p = 0.19). There were no differences in the patient-reported outcome measures. Participants reported poor quality sleep during both closed-loop and sensor-augmented pump therapy treatment phases (PSQI Total Sleep Quality Score 5.0 during closed-loop, 5.5 during sensor-augmented pump therapy, p = 0.78; PSQI sleep quality score ≥5 indicates poor sleep quality). Most participants (>80% at the end of both phases) reported less fear of nocturnal hypoglycaemia, although over a third experienced ongoing worry or fear about low blood sugars during sleep.

Table 3.6: Measurements of sleep during the randomised crossover trial

Actigraphy measurements			
	Sensor-augmented pump therapy	**Closed-loop therapy**	**P-value**
Mean sleep duration (hours); mean (SD)	7.1 (1.2)	7.5 (0.8)	0.22
Mean sleep efficiency (%); mean (SD)	80.5 (7.9)	84.2 (3.8)	0.19
Mean Wake After Sleep Onset (minutes); mean (SD)	51.3 (22.3)	46.3 (15.8)	0.44
Mean number of awakenings; mean (SD)	51.5 (14.6)	57.5 (15.4)	0.23
Pittsburgh Sleep Quality Index (PSQI)			
Total sleep quality score*	5.5 (5.0, 6.0)	5.0 (3.75, 6.5)	0.78
Sleep disturbance±	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.73
Daytime dysfunction‡	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	0.17

*PSQI sleep quality score ≥5 indicates poor sleep quality, <5 indicates good sleep quality

± PSQI sleep disturbance score 0 indicates minimal sleep disturbance, 3 indicates very disturbed sleep

‡PSQI daytime dysfunction score 0 indicates minimal daytime dysfunction, 3 indicates marked daytime dysfunction

3.4.4 Adverse events

There were no reportable serious adverse events but there were frequent device deficiencies, most frequently, involving the closed-loop mobile phone (47%) and CGM (30%) devices (Table 3.7).

Table 3.7: Breakdown of device deficiencies during the randomised crossover trial

Type of device deficiency	**SAP**	**CL**	**Follow up phase**	**Number of events**
Continuous glucose monitor or connectivity	8	9	19	36
Insulin pump	4	3	9	16
Closed-loop mobile phone	1	18	38	57
Difficulty downloading devices	2	4	6	12

None of the device deficiencies resulted in severe hypo or hyperglycaemia or other adverse clinical outcomes.

There were no reportable serious adverse events (SAEs) recorded during the randomised trial.

3.4.5 Antenatal closed-loop feasibility

All of the study participants elected to continue using the closed-loop system for at least some of the time after completion of the randomised crossover study. Participants maintained a median glucose of 6.9, 6.7, and 6.6 mmol/L at 28-32, 32-36 and >36 weeks gestation respectively. The median time spent with target glucose concentrations was 70.6, 71.5, and 72.3% at 28-32, 32-36, and >36 weeks gestation (Table 3.8, Figure 3.4). Exposure to hypoglycaemia was low throughout the follow up phase, with participants spending a median of 1.9-2.3% of the time with glucose concentrations below 3.5 mmol/L. Participants using the closed-loop system wore their sensors for a median of 22.4, 19.9, and 21.7 hours per day at 28-32, 32-36, and >36 weeks gestation.

One participant (Participant 8) travelled to the Middle East for eight weeks without contact or antenatal care. Another (Participant 15) relocated to Australia, and continued closed-loop therapy until delivery. Details of each individual participant's glucose control are presented in Table 3.9.

Table 3.8: Glycaemic control using closed-loop during the follow up phase (end of the randomised crossover trial until delivery)

	Number of weeks gestation		
	28-32 n=8	**32-36 n=16**	**>36 n=9**
% time in target (3.5-7.8 mmol/L)	70.6 (64.2, 75.4)	71.5 (68.9,75.9)	72.3 (67.3, 80.3)
% time >7.8 mmol/L	28.0 (23.0, 34.0)	24.4 (22.8, 29.3)	23.7 (17.7, 31.5)
% time <3.5 mmol/L	1.9 (1.7, 2.3)	2.0 (1.1, 3.9)	2.3 (1.0, 3.0)
Mean glucose (mmol/L)	6.9 (6.6, 7.2)	6.7 (6.4, 6.9)	6.6 (6.4, 6.9)
Sensor wear (hours/day)	22.4 (11.3, 23.2)	19.9 (15.1, 23.0)	

Data are median (interquartile range)

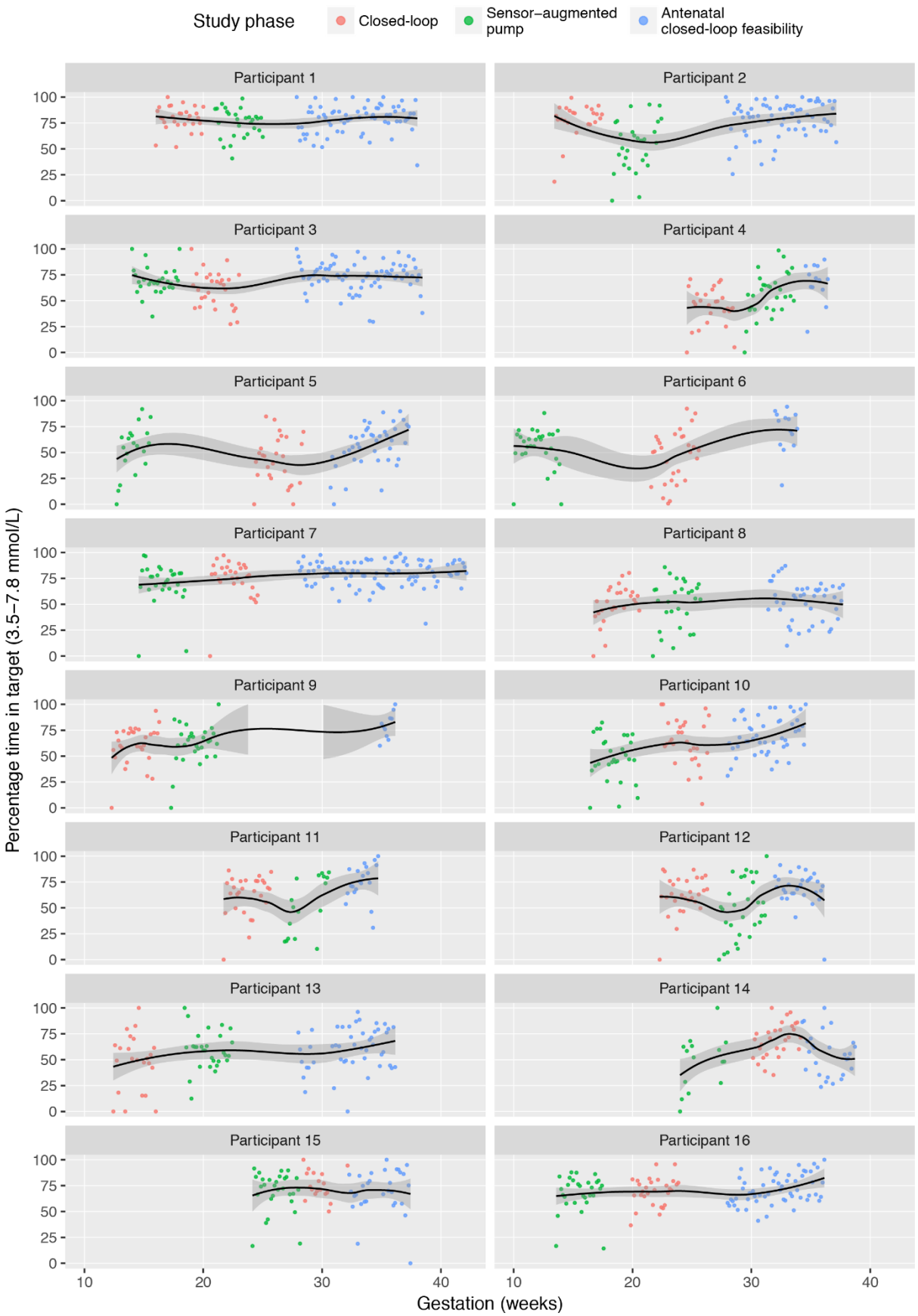


Figure 3.4: Glucose control of individual participants during the closed-loop and sensor augmented pump phases of the randomised crossover trial, and during antenatal follow-up until delivery

Table 3.9: Glycaemic control by participant during the randomised crossover trial and antenatal closed-loop feasibility phase

Participant ID	Insulin delivery	Booking HbA1c	CGM and HbA1c measures	SAP Control	CL	28-32 weeks	32-36 weeks	36 weeks-delivery
1	CSII	56 mmol/mol 7.3%	% time in target (3.5-7.8 mmol/L)	76.1	80.3	75.3	80.9	80.3
			% time >7.8 mmol/L	22.6	18.5	23.3	17.9	16.8
			% time <3.5 mmol/L	0.8	0.8	1.5	1.2	3.0
			Mean glucose (mmol/L)	6.7	6.5	6.6	6.3	6.3
			HbA1c (mmol/mol)	41	40		44	
2	MDI	65 mmol/mol 8.1%	% time in target (3.5-7.8 mmol/L)	55.0	80.4	74.3	82.1	81.4
			% time >7.8 mmol/L	43.9	17.5	23.3	15.4	17.7
			% time <3.5 mmol/L	1.1	1.8	2.1	2.4	0.9
			Mean glucose (mmol/L)	7.6	6.4	6.6	6.2	6.4
			HbA1c (mmol/mol)	43	46		43	48
3	CSII	50 mmol/mol 6.7%	% time in target (3.5-7.8 mmol/L)	68.8	58.3	75.6	69.8	76.0
			% time >7.8 mmol/L	28.7	42.1	22.2	29.0	22.0
			% time <3.5 mmol/L	2.4	0.6	2.1	1.1	2.0
			Mean glucose (mmol/L)	6.8	7.6	6.6	6.9	6.6
			HbA1c (mmol/mol)	47	45	45	47	49
4	MDI	86 mmol/mol 10.0%	% time in target (3.5-7.8 mmol/L)	57.9	45.2		67.4	67.3
			% time >7.8 mmol/L	39.6	54.7		30.2	31.8
			% time <3.5 mmol/L	1.0	1.1		2.3	1.0
			Mean glucose (mmol/L)	7.4	8.3		7.1	7.4
			HbA1c (mmol/mol)	54	52			
5	CSII	64 mmol/mol 8.0%	% time in target (3.5-7.8 mmol/L)	55.9	43.4		57.8	66.1
			% time >7.8 mmol/L	41.1	55.3		41.3	31.5
			% time <3.5 mmol/L	3.2	2.3		1.0	2.5
			Mean glucose (mmol/L)	7.8	8.3		7.6	6.9
			HbA1c (mmol/mol)	49	53		56	

			% time in target (3.5-7.8 mmol/L)	56.7	54.2		69.7	72.3
6	MDI	85 mmol/mol	% time >7.8 mmol/L	40.1	55.0		21.7	25.4
		9.8%	% time <3.5 mmol/L	1.7	0.8		8.6	2.3
			Mean glucose (mmol/L)	7.6	8.6		6.2	6.4
			HbA1c (mmol/mol)	50	51		52	53
			% time in target (3.5-7.8 mmol/L)	72.8	77.7	80.6	77.4	82.7
7	CSII	55 mmol/mol	% time >7.8 mmol/L	23.0	19.3	17.1	17.8	10.4
		7.2%	% time <3.5 mmol/L	4.1	2.2	2.3	4.8	6.9
			Mean glucose (mmol/L)	6.4	6.3	6.3	6.1	5.7
			HbA1c (mmol/mol)	43	43		45	46
			% time in target (3.5-7.8 mmol/L)	52.9	50.9	71.7	56.1	56.8
8*	MDI	83 mmol/mol	% time >7.8 mmol/L	42.5	46.7	27.4	43.2	42.5
		9.7%	% time <3.5 mmol/L	3.0	1.5	0.9	0.7	0.7
			Mean glucose (mmol/L)	7.9	7.9	7.1	7.8	7.8
			HbA1c (mmol/mol)	34	41		36	31
			% time in target (3.5-7.8 mmol/L)	64.2	62.5		76.4	
9	MDI	68 mmol/mol	% time >7.8 mmol/L	35.9	35.4		23.2	
		8.4%	% time <3.5 mmol/L	0.6	0.4		0.3	
			Mean glucose (mmol/L)	7.4	7.4		6.8	
			HbA1c (mmol/mol)	49	50		45	
			% time in target (3.5-7.8 mmol/L)	50.2	62.8	65.1	74.9	
10	CSII	60 mmol/mol	% time >7.8 mmol/L	48.4	35.1	33.2	23.4	
		7.6%	% time <3.5 mmol/L	1.4	1.2	1.7	1.7	
			Mean glucose (mmol/L)	8.1	7.5	7.1	6.6	
			HbA1c (mmol/mol)	45	45			
			% time in target (3.5-7.8 mmol/L)	48.6	64.6		73.2	
11	MDI	56 mmol/mol	% time >7.8 mmol/L	51.0	33.7		23.1	
		7.3%	% time <3.5 mmol/L	0.4	1.6		3.7	
			Mean glucose (mmol/L)	8.1	7.2		6.5	

			HbA1c (mmol/mol)	54	49			
			% time in target (3.5-7.8 mmol/L)	50.2	63.2		71.7	
12	CSII	60 mmol/mol	% time >7.8 mmol/L	49.0	35.9		26.7	
		7.6%	% time <3.5 mmol/L	0.2	0.5		1.6	
			Mean glucose (mmol/L)	7.8	7.3		6.8	
			HbA1c (mmol/mol)	50	48			
			% time in target (3.5-7.8 mmol/L)	58.5	47.5	54.6	64.7	
13	MDI	65 mmol/mol	% time >7.8 mmol/L	32.5	50.1	40.5	30.4	
		8.1%	% time <3.5 mmol/L	9.0	3.1	4.9	4.8	
			Mean glucose (mmol/L)	6.8	7.9	7.5	7.0	
			HbA1c (mmol/mol)	50	57	48	56	57
			% time in target (3.5-7.8 mmol/L)	52.1	69.6	61.8	69.4	
14[±]	CSII	57 mmol/mol	% time >7.8 mmol/L	39.8	27.6	36.5	26.3	
		7.4%	% time <3.5 mmol/L	5.7	2.7	1.7	4.2	
			Mean glucose (mmol/L)	7.6	6.8	7.4	6.6	
			HbA1c (mmol/mol)	44	44			
			% time in target (3.5-7.8 mmol/L)	71.8	74.4		71.3	71.7
15	MDI	52 mmol/mol	% time >7.8 mmol/L	20.9	22.4		25.0	23.7
		6.9%	% time <3.5 mmol/L	7.0	3.2		3.7	4.5
			Mean glucose (mmol/L)	6.3	6.5		6.7	6.8
			HbA1c (mmol/mol)	40	39			
			% time in target (3.5-7.8 mmol/L)	69.8	71.2	66.9	75.7	
16	CSII	57 mmol/mol	% time >7.8 mmol/L	28.7	27.5	32.6	23.8	
		7.4%	% time <3.5 mmol/L	1.4	1.3	0.5	0.6	
			Mean glucose (mmol/L)	6.9	6.7	7.1	6.7	
			HbA1c (mmol/mol)	41	37	41	43	

[*]This participant travelled to the Middle East, for eight weeks without adequate contact or antenatal care

[±] This participant relocated to Australia immediately after the randomised crossover trial, and continued to use closed-loop

3.4.6 Post-partum closed-loop feasibility

After delivery, 12 participants chose to continue using closed-loop insulin delivery for up to six weeks post-partum. They maintained safe glucose control, with 77.1% time-in-target (3.9-10.0 mmol/L) and minimal hypoglycaemia (2.3% of time less than 3.9 mmol/L) during the first 6 weeks post-partum (Tables 3.10 and 3.11). Sensor wear was particularly variable during this period, with participants wearing the sensors for a median of 16.5 hours per day (range 1.3 to 21.9 hours; Table 3.11). Where sensor wear was low it was generally the case that a participant wore the sensors intensively for the lifespan of a sensor, with prolonged gaps between the expiry of one sensor and reinsertion of a new one.

Table 3.10: Glycaemic control during the post-partum closed-loop feasibility phase; (delivery to 6 weeks post-partum)

	n=12
% time in target (3.9-10 mmol/L)*	77.1 (75.1, 90.4)
% time >10.0 mmol/L	22.1 (9.5, 24.4)
% time <3.9 mmol/L	2.4 (0.8, 3.7)
Mean glucose (mmol/L)	7.7 (7.1, 8.2)
Sensor wear (hours/day)	16.5 (11.6, 19.2)

*The glucose target range was 3.9-10.0 mmol/L after delivery.

3.11: Post-partum glycaemic control by participant in the 12 participants who choose to use closed-loop after delivery and for up to 6 weeks post-partum

Participant number[±]	**Mean sensor wear (hours/day)**	**Mean glucose (mmol/L)**	**% time in target**[*] **(3.9-10.0 mmol/L)**	**% time >10.0 mmol/L**	**% time <3.9 mmol/L**
1	12.3	7.3	90.0	9.6	0.4
2	18.5	8.2	75.6	23.8	0.6
3	14.9	8.2	75.4	23.8	0.8
4	16.2	8.0	75.2	21.2	3.6
5	1.3	6.9	95.0	5.0	0
7	21.2	5.8	95.4	3.2	1.5
9	2.0	6.7	91.6	5.4	3.0
10	22.0	8.2	73.1	23.3	3.6
11	16.8	7.9	75.0	20.9	4.1
13	21.9	8.6	70.0	28.3	1.7
14	9.6	7.6	78.6	16.0	5.4
16	18.1	7.2	88.2	10.9	0.9

[*]The glucose target range was adjusted to 3.9-10.0 mmol/L after delivery.

[±]These data are for the 12 out of 16 (75%) participants who chose to use closed-loop for at least some of the time after delivery.

3.4.7 Obstetric and neonatal outcomes

Participants delivered at a median (interquartile range) gestation of 36.9 (36.1, 37.8) weeks gestation. Thirteen women delivered via caesarean section, seven of which occurred prior to the onset of labour. Two participants developed pre-eclampsia. One participant had a placental abruption. Median (interquartile range) birthweight was 3575g (3055, 3685). Seven neonates (44%) were born large-for-gestational age, with five having a birthweight above the 97th centile. One neonate was small-for-gestational age (birthweight 2880g). Eleven (69%) of the 16 infants were admitted to the neonatal intensive care unit (NICU), with seven (44%) requiring treatment for neonatal hypoglycaemia.

Two infants had congenital anomalies. One had a neural tube defect (lumbar/sacral lipomyelomeningocele) detected post-partum. This woman (Participant 2) had an unplanned pregnancy (booking HbA1c 8.1%), switched from MDI to closed-loop therapy with good effect, and maintained excellent glucose control throughout pregnancy. Another infant had severe unilateral hydronephrosis (10 mm renal pelviceal dilatation detected at 20 weeks gestation). The mother of this infant conceived spontaneously after four unsuccessful cycles of IVF (booking HbA1c 9.7%). She also switched from MDI to closed-loop therapy, with a striking fall in HbA1c (5.0%) despite modest time-in-target (56%) in late pregnancy (Table 3.9, Participant 8). Individual obstetric and neonatal outcomes are presented in Table 3.12.

Table 3.12: Individual obstetric and neonatal outcomes with details of past obstetric and medical conditions

Participant number	Gravidity	Parity	Obstetric history	Medical history	Delivery Gestation	Antenatal steroids	Mode of delivery	Birthweight of infant (g)	Neonatal hypoglycaemia	Neonatal intensive care unit	Obstetric and neonatal complications
1	2	0	1 miscarriage	N/A	38+0	No	Vaginal	3680	No	No	No
2	2	1	1 live birth	N/A	37+1	No	C-section	2970	No	No	Neural tube defect (lipomyelo-meningocele)
3	1	0	N/A	N/A	38+3	No	C-section	4035	No	No	No
4	2	1	1 live birth	N/A	36+3	No	C-section	4005	Yes	Yes	Placental abruption, Neonatal jaundice
5	4	2	2 live births, 1 congenital anomaly/ TOP	N/A	37+2	Yes	C-section	3910	Yes	Yes	Neonatal hypoglycaemia
6	3	1	1 live birth, 1 miscarriage	Hepatitis C, Retinopathy, Depression, Hypothyroid,	36+6	No	C-section	3345	No	Yes	Transitional care for observation only
7	4	1	1 live birth, 1 miscarriage, 1 TOP	N/A	38+4	No	Vaginal	2880	No	No	No

8	4	1	1 live birth, 2 miscarriages	4 x failed IVF, Retinopathy	37+5	No	C-section	3600	No	No	Hydronephrosis, Pre-eclampsia
9	1	0	N/A	N/A	36+1	Yes	C-section	3550	Yes	Yes	Pre-eclampsia, Post-partum haemorrhage, Neonatal respiratory distress, jaundice
10	1	0	N/A	N/A	34+2	Yes	C-section	3665	Yes	Yes	Neonatal respiratory distress & sepsis
11	1	0	N/A	N/A	34+4	Yes	C-section	2940	Yes	Yes	Neonatal hypoglycaemia
12	2	1	1 live birth	Retinopathy, Hypothyroid	37+0	No	C-section	4010	No	Yes	Neonatal respiratory distress
13	3	2	2 live births, Gestational hypertension, Post-natal depression	Depression	36+2	No	Vaginal	3690	No	Yes	Neonatal sepsis
14	3	1	1 Stillbirth, 1 miscarriage	N/A	34+3	Yes	C-section	3375	Yes	Yes	Neonatal jaundice & respiratory distress
15	1	0	N/A	Endometriosis, asthma, IVF	38+1	No	C-section	3090	Yes	Yes	Neonatal hypoglycaemia
16	2	1	1 live birth	Hypertension, Retinopathy	36+0	Yes	C-section	3020	No	Yes	Neonatal jaundice

TOP = Termination of Pregnancy, IVF = In Vitro Fertilisation

3.4.8 Inter-individual variability

The individual participant data highlights variability in women's glycaemic responses to closed-loop (Figure 3.4, Table 3.9). This does not appear to be related to previous technology use as glycaemic control was comparable in participants who used insulin pumps or MDI at enrolment (Table 3.5). Five participants, including two pump (Participants 3 and 5) and three MDI users (Participants 4, 6, and 13) had ≥10% lower time-in-target range during the randomised closed-loop crossover, although they all continued to use closed-loop, with higher time-in-target, in later pregnancy.

Post hoc analyses suggested that participants with lower booking HbA1c levels (≤7.5%) had higher time-in-target both during closed-loop and sensor-augmented pump study phases, compared to those with HbA1c>7.5%. This pattern persisted throughout pregnancy, including after 36 weeks, when participants with lower HbA1c maintained near-optimal glucose control (mean glucose 6.4 mmol/L, 77.7% time-in-target). Participants with booking HbA1c>7.5% had higher mean glucose and lower time-in-target, even after 36 weeks, (7.0 mmol/L, 68.8% time-in-target; Table 3.13).

Table 3.13: Glycaemic control during the randomised crossover trial and antenatal closed-loop feasibility phase in participants with HbA1c levels≤7.5% or >7.5% (58 mmol/mol) at enrolment

	Booking HbA1c ≤7.5% (n=7)						**Booking HbA1c >7.5% (n=9)**					
	Sensor-augmented pump	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**	**Sensor-augmented pump**	**Closed-loop**	**Difference (CL-SAP)**	**28-32 weeks**	**32-36 weeks**	**>36 weeks**
% Time in target (3.5-7.8 mmol/L)	69.1*	72.1*	3	72.0	74.0	77.7*	57.0*	57.3*	0.3	64.6	69.0	68.8*
% Time below 3.5 mmol/L	1.0	0	-1.0	1.6	2.7	4.1*	0	0.2	0.2	3.0	2.6	1.5*
Mean glucose (mmol/L)	6.8*	6.7*	-0.1	6.8	6.5	6.4*	7.6*	7.9*	0.3	7.1	6.9	7.0*

*Indicates significant difference between participants with HbA1c ≤7.5% compared with booking HbA1c >7.5% ($p<0.05$)

3.5 Discussion

We found that day-and-night closed-loop was safe, feasible, and could effectively control glucose in a broad range of pregnant women with type 1 diabetes. Participants achieved comparable glycaemic control during the randomised sensor-augmented pump and closed-loop phases, with no difference in percentage time-in-target, sensor glucose, or HbA1c. However, there was a reduction in both frequency of hypoglycaemic events and exposure to hypoglycaemia during closed-loop. There were no episodes of severe hypoglycaemia during the crossover trial or throughout pregnancy.

Previous evaluations of closed-loop (173,191), including our study of overnight closed-loop in pregnancy (presented in Chapter 2), found that closed-loop was associated with higher time-in-target compared to sensor-augmented pump therapy. There are several potential explanations for our current findings. Firstly, the level of glucose control achieved with sensor-augmented pump therapy (60% in 3.5-7.8 mmol/L range, 82.5% in 3.9-10.0 mmol/L non-pregnant range) was considerably higher than in previous studies (173,191,228). A recent systematic review found that closed-loop was associated with a 12.6% increased time-in-range where the comparator (sensor-augmented pump in 21/22 single hormone studies), spent 58% time-in-range (3.9-10.0 mmol/L)(228). Therefore, the glucose control achieved with sensor-augmented pump in our study was comparable to that achieved with closed-loop in previous studies (173,191), including in well-controlled adults (HbA1c <7.5%; (186)), perhaps reducing the potential for further improvement. An appropriate goal of closed-loop in well-controlled participants may be to reduce the burden of hypoglycaemia without deterioration in glucose control (186,237), which appears consistent with our findings in this study, though not in the study presented in Chapter 2.

Secondly, we consciously enrolled a diverse population for this study, including participants of varied technology experience, diabetes education and glycaemic control. The majority were technology-naïve with over 80% sensor-naïve and 50% pump-naïve at enrolment. Over half of our participants had booking HbA1c levels above 7.5%,

representing suboptimal glucose control at conception and perhaps a lower degree of engagement with diabetes and pre-pregnancy services. Among the five participants with lower time-in-target during closed-loop, one cycled 30 to 60 minutes twice daily and struggled to avoid post-exercise hypoglycaemia (Participant 3), while another worked night shifts during closed-loop (Participant 4). These differences in lifestyle patterns appear to represent an ongoing challenge for the closed-loop system. Three participants (4, 6, 13) were frequent non-attenders at antenatal clinics and had minimal contact with the study team. They used closed-loop variably, although all three used it to good effect in late gestation.

The influence of lifestyle and behavioural factors during closed-loop is not well understood. Recent data suggest that behavioural factors, including snacking, account for approximately one third of the intra-individual variability in glucose concentration during closed-loop (238). The frequency of manual bolusing is also important, emphasising the need for ongoing diabetes education and support, in conjunction with closed-loop (239). Others have commented that closed-loop may have unintended impacts on dietary intake, proposing that education to optimise healthy eating patterns should be incorporated into closed-loop training programmes (240). The frequency of manual boluses and dietary patterns of participants are not available for our study.

Previous qualitative research suggests that some participants may have unrealistic expectations, placing too much trust in closed-loop and becoming more passive in their self-management (241). This was echoed by pre-trial comments from current participants; "The way I see it is literally this app on this phone is literally going to take my brain away basically, which is happy days" (Participant 4). During the baseline qualitative interview, she reflected on her motivation to participate, which was in part, to avoid capillary glucose testing: "I'm not the best with blood tests but that's because I kind of more or less listen to the symptoms of highs and lows rather than doing a test, which is naughty, but that's the reason I wanted to go on the CLIP." Device difficulties notwithstanding, other investigators have reported that current "closed-loop/artificial pancreas" terminology may imply a more "hands-off" approach (242). Perhaps this means that while participants spend substantial time thinking about their diabetes (as

discussed in Chapter 4), they might be less proactive in their diabetes self-management, instead relying on the closed-loop system to control glycaemia.

While sensor use was generally high (approximately 20 of 24 hours), use of closed-loop during the randomised crossover trial was affected by technical problems that frequently required closed-loop to be reset. The algorithm is adaptive, meaning that its performance improves for an individual participant over time. System errors were often addressed quickly by phone. However, a problem requiring that the system be reset meant that the algorithm returned to participant-naïve parameters. Technical issues may have reduced participants' trust, which may also have contributed to participants being tempted to override the closed-loop algorithm advice (243).

Throughout antenatal follow-up, participants achieved good overall glycaemic control (70.6-72.3% time-in-target). This is comparable to the glucose control in our overnight closed-loop trial, conducted in well-controlled participants (baseline HbA1c 6.6%, presented in Chapter 2). It is 10% higher than the control group in the CONCEPTT trial of CGM in pregnancy (61% time-in-target) and slightly higher than the CGM group of that study, which spent 68% time-in-target range (150). The CONCEPTT CGM group had substantially more hypoglycaemia with 4% time <3.5 mmol/L and 3.5 hypoglycaemia episodes a week. Taken together, these data suggest that closed-loop facilitates good day-to-day glucose control in a broad patient population, and is effective for minimising risk of hypoglycaemia. There were no episodes of severe hypoglycaemia during the current or previous closed-loop pregnancy trials. We also found that, despite frequent technical difficulties with devices, 75% of women continued closed-loop after delivery and for up to 6 weeks post-partum.

The obstetric and neonatal outcomes remain suboptimal, suggesting that while the burden of maternal hypoglycaemia can be minimised, excessive fetal exposure to maternal hyperglycaemia persists. More research is needed to address the potentially modifiable dietary and snacking behaviours that contribute to post-prandial hyperglycaemia and are still challenging during closed-loop.

Strengths of this study include the randomised crossover design, which allows each participant to function as their own control, eliminating inter-individual variability in insulin sensitivity, dietary intake, and exercise patterns. The analyses were performed as intention-to-treat regardless of closed-loop compliance, and the randomised order of study phases reduces the impact of gestation or the order of interventions. The closed-loop system we used in this study used commercially available insulin pumps and CGM that were consistent in both study arms. Housing the closed-loop algorithm on a mobile phone meant that this system was more portable than those that have been used in previous studies. Participants were recruited from three NHS sites, and included women without diabetes technology experience and with a wide range of glucose control. We did not use remote monitoring or restrict participants' dietary habits, exercise or travel rendering the study as "real-world" as possible.

However, we also acknowledge the limitations. The relatively short four-week duration may have been insufficient for optimal training particularly for device-naïve participants and those with less advanced diabetes self-management skills. The crossover study design may also have been less suitable for participants with variable lifestyles (e.g., night workers, those travelling overseas). While the prototype closed-loop system was portable and generally well received, it had frequent errors, increasing the need for troubleshooting and support from the research team. This frustrated participants and reduced the time that closed-loop was operational. The control group of sensor-augmented pump did not have the option of suspending insulin delivery during low or predicted low glucose concentration. Unfortunately, we do not have data regarding dietary intake or accurate measures of closed-loop compliance.

In this cohort of pregnant women with type 1 diabetes, with a broad range of glucose control, closed-loop was as effective as sensor-augmented pump therapy, but potentially safer because closed-loop reduced the extent and duration of hypoglycaemia. It is difficult to know whether similar reductions in hypoglycaemia could have been achieved using a low glucose suspend system. More research is needed to improve glucose control in postprandial times including the impact of exercise programs, dietary changes and

faster acting insulin analogues. Further, it will be important to develop closed-loop training programmes to support optimal self-management behaviours including diet, exercise, insulin dose adjustment, and interpretation of CGM readings, particularly for women who enter pregnancy with higher HbA1c. More detailed analyses of the results of the current study and that presented in Chapter 2 may assist prediction of users likely to benefit from the use of closed-loop therapy so that it can be correctly targeted when it becomes commercially available.

3.6 Conclusion

In the crossover phase of this trial, we demonstrated the safety and feasibility of day and night closed-loop insulin delivery in the home setting. Closed-loop therapy was associated with similar mean glucose levels and percentage time with target glucose levels, but less hypoglycaemia, compared to sensor-augmented pump therapy. All 16 participants elected to continue using day-and-night closed-loop therapy during at least part of the follow-up phase. They achieved 70.6-72.3% time-in-target during the antenatal follow up phase. However, technical and device issues will need to be addressed before this system can be more widely used.

4. Experiences of closed-loop insulin delivery in pregnancy

4.1 Background

Pregnancy in women with type 1 diabetes is associated with increased risk of adverse outcomes, with two- to fivefold increased risk of congenital anomaly, stillbirth and neonatal death compared with the background maternity population (49,58,244,245). These and other diabetes-related risks can be minimised with strict glucose control before and during pregnancy (66). Pregnant women with type 1 diabetes are therefore highly motivated to improve their glucose control, and are unlike almost any other group of people with diabetes in terms of sustained effort and motivation. At this highly motivated life stage, they tend to invest more time and effort to optimise dietary intake, glucose monitoring, and insulin dose adjustment than at any other time during their decades of living with diabetes. They have frequent clinical contacts (typically every one to two weeks) with specialist antenatal diabetes pregnancy healthcare teams. Despite these intensive efforts, pregnant women with type 1 diabetes spend only 12 hours per day with near-optimum glucose control (8), and rates of preterm delivery, macrosomia and neonatal intensive care unit admissions remain high (49,246). Unsurprisingly, this sustained effort, and the difficulty in achieving and maintaining optimum glucose control, can affect psychosocial wellbeing.

Previous psychosocial research describes pregnant women with type 1 diabetes alternating between having "mastery" of their condition and being "enslaved" by it (247).

Technology to help pregnant women with type 1 diabetes improve glucose control, such as continuous glucose monitoring (CGM) and insulin pump therapy, is constantly evolving (124,150). More recently, closed-loop systems have been introduced (13,14). Hybrid closed-loop systems still require carbohydrate counting and manually administered pre-meal boluses, but they incorporate computer algorithms to provide automated, glucose-responsive basal insulin delivery every 10 to 15 minutes (248). Conventional insulin pumps typically provide four to six pre-programmed basal rates, which are adjusted based on capillary glucose profiles. The addition of CGM to continuous subcutaneous insulin infusion (sensor-augmented pump therapy) facilitates more glucose-responsive insulin delivery, but in practice many women struggle with the sheer volume of minute-to-minute CGM data and the complexity of insulin dose adjustment (145). By assuming a substantial burden of basal insulin adjustment, automated closed-loop systems have the potential to improve glucose control in type 1 diabetes pregnancy (229), but their psychosocial impact is unknown. The aim of the present study was to explore pregnant women's experiences of automated closed-loop therapy overnight and over an extended period of daytime use, in addition to their perceptions of glycaemic control and wider attitudes to technology.

4.2 Aim

To explore the experiences of pregnant women with type 1 diabetes, and the relationships between perceptions of glucose control, attitudes to technology and glycaemic responses with regards to closed-loop insulin delivery.

4.3 Methods

Between April 2014 and December 2015 we performed an open-label, randomised, crossover trial incorporating both biomedical (maternal glycaemic and obstetric/neonatal health outcomes) and psychosocial evaluations. Full details of the study design and biomedical outcomes are reported in Chapter 2. In brief, after two to four weeks of device training, women were randomly assigned to either four weeks of overnight closed-loop or four weeks of user-directed sensor-augmented pump therapy, with a two-week washout between study phases. Pre-meal boluses were manually administered using the study pump (DANA Diabecare R Insulin Pump; SOOIL, Seoul, Korea) bolus calculator in both phases.

During closed-loop therapy, a computer algorithm, housed on a tablet computer, used CGM glucose values to calculate an appropriate basal insulin dose, which was delivered via an insulin pump every 12 minutes (Figure 4.1). Women were instructed only to use closed-loop therapy overnight, turning it on after their evening meal and switching it off before breakfast. During a follow-up phase, women could choose to continue sensor-augmented pump or closed-loop therapy during the day and night. Of the 16 participants,14 opted to use day-and-night closed-loop therapy, providing data for an additional median (interquartile range) 11.6 (7.1, 12.7) weeks.

Pregnant women, aged 18 to 45 years and with booking HbA1c levels of 48 to 86 mmol/mol (6.5 to 10%), were recruited at between eight and 24 weeks' gestation from three UK National Health Service (NHS) sites. All were using intensive insulin therapy administered either by multiple daily injections (n = 6) or continuous subcutaneous insulin infusion (n = 10) before pregnancy. Key exclusion criteria were multiple pregnancy and severe physical or psychiatric comorbidity. All participants provided written informed consent.

The primary outcome for the randomised trial was the percentage of time that women spent with their glucose concentration in the target range of 3.5 to 7.8 mmol/L

overnight, as recorded by the study CGM FreeStyle Navigator II (Abbott Diabetes Care, Witney, UK) during each four-week crossover phase. The objective glycaemic response was described as the relative difference in overnight time-in-target during each four-week crossover period.

Figure 4.1: Image of participants wearing the closed-loop system

An individually adaptive control algorithm is housed on a tablet computer and uses glucose readings from the continuous glucose monitor to adjust insulin delivery via the insulin pump every 12 minutes when closed-loop is turned on.

4.3.1 User-reported outcomes

Participants completed the Diabetes Technology Questionnaire (DTQ) "standard" version (Appendix C) and the Hypoglycaemia Fear Survey II (HFS-II; Appendix D) at baseline (n=16). The DTQ standard version is a 30-item measure of the impact of and satisfaction with current diabetes technology (249). Participants repeated the HFS-II and completed the "change" version of the DTQ to account for any ceiling effect within seven days of closed-loop (n = 11 for DTQ and n = 10 for HFS) and sensor-augmented pump (n = 12 for both HFS and DTQ). The change version of the DTQ was used to evaluate the impact of the current treatment, as compared with previous treatment (i.e., sensor-augmented pump therapy vs automated closed-loop therapy). Higher scores indicate higher treatment satisfaction. The HFS-II questionnaire consists of a 10-item "behaviour" subscale that measures behaviours involved in avoidance and overtreatment of hypoglycaemia and a 13-item "worry" subscale that measures anxiety and fear surrounding hypoglycaemia (250). Higher scores indicate higher fear of hypoglycaemia.

4.3.2 Qualitative interviews

We administered semi-structured interviews according to a topic guide developed from reviewing relevant literature (Appendix E). We interviewed women twice: at baseline during device training (T1) and after completion of the study (T2; mean gestation 14.6 and 27.7 weeks, respectively). This provided an opportunity to explore experiences of closed-loop therapy over a longer timeframe.

For clinical and logistical reasons, two participants were not interviewed at follow-up (severe pre-eclampsia and emergency caesarean delivery) and one participant was interviewed at follow-up only, thus providing data from 27 interviews with 14 women. In line with previous qualitative interview studies (251), we found this sample sufficient to attain data saturation (i.e., the point in data collection when no new data are found to develop emerging conceptual themes).

Interviews were conducted in person, in clinical settings (n = 13), at participants' homes (n = 8), or by telephone (n = 6). Interviews were digitally recorded and transcribed verbatim. The interviews lasted on average 26.5 and 32.5 minutes (baseline and follow-up, respectively). Interview transcripts were coded using NVIVO software (QSR International Pty Ltd., Version 10, 2012, Daresbury, UK). Three investigators identified key themes relating to the burdens and benefits of diabetes technology using a six-stage thematic analysis approach: familiarisation with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing a final analysis (252). Our approach was informed by theories of sensemaking, according to which experience is influenced by users' preceding experiences, attitudes, and values in conjunction with technological "affordances", or capacities (253,254).

We supplemented this with framework analysis, a method involving the use of a matrix with cells into which summary data are entered by category (columns) and cases (rows; Table 4.4). In the context of this study, this allowed us to present data on how individuals responded to closed-loop insulin delivery in terms of two categories: (1) biomedical data (i.e. level of glycaemic control, rated on a 1 to 5 scale); and (2) quantised psychosocial data, also rated on a 1 to 5 scale, referring to: women's opinions of their glycaemic control, disparities between women's opinions and the biomedical data, women's opinions towards technology, and changes in women's attitudes to technology over time.

For the framework analysis, psychosocial interview data were quantised by coding comments about perceived glucose control as entirely positive or negative, mostly positive or negative, or mixed. This coding method drew on the sentiment analysis approach, in which language is examined for underlying emotional content, and positive and negative content in particular (255). Women's views about technology were categorised in the same way.

Our analytical approach to qualitative data thus allowed us to identify new and unforeseen themes inductively (thematic analysis) as well as deductively eliciting participants' opinions on desired topics of relevance to diabetes technology use

(framework analysis). This, in turn, allowed a flexible mixed-methods approach to exploring both individual and collective data.

4.4 Results

4.4.1 Benefits of closed-loop therapy

The questionnaire data suggested a range of potential benefits from closed-loop therapy, ranging from improved glucose control to reduced worry, reduced discomfort, and "time off" from diabetes (Table 4.1). Worry about hypoglycaemia during sleep was improved among eight participants, with seven reporting that less effort was required to prevent hypoglycaemia during sleep. Women using closed-loop therapy also reported some modest benefit in terms of pain or discomfort from insulin injections or pumps (three better), family arguments about diabetes (two better), pain from fingerpricks or sensors (two better) and getting the insulin dose right on sick days (three better).

Table 4.1: Changes in Diabetes Technology Questionnaire and Hypoglycaemia Fear Survey II (HFS II) scores during closed-loop (CL) and sensor-augmented pump therapy (SAP)

	DTQ (*n* = 11)		HFS II (*n* = 10)*		
	Current problem	Change	Total	Behaviour	Worry
Baseline (*n* = 16)	3.6 (0.7)		62.3 (13.2)	30.6 (5.4)	31.7 (9.9)
End of SAP (*n* = 12)	3.6 (1.0)	3.6 (0.5)	60.5 (10.4)	30.8 (6.0)	30.0 (7.4)
End of CL (*n* = 11)	3.1 (0.8)	3.3 (0.3)	60.8 (11.3)	29.4 (4.8)	30.6 (7.0)

DTQ, Diabetes Technology Questionnaire

*There were no statistically significant differences between cohorts on the DTQ or HFS II, either as a total score or on either behaviour or worry subscale.

The interview data confirmed the questionnaire data with regards to glucose control, improved sleep, reassurance for users and family members and 'time off' from diabetes (Table 4.2). The notion of "time off" was often expressed in terms of perceived normality: "I'm less worried and less anxious about [diabetes]. . . and I'm just feeling a bit more normal" (T2, Participant 6) – or, relatedly, in terms of having a system that replicates a fully-functioning pancreas: "this study . . . mimics what a pancreas does" (T2, Participant 16).

The more wide-ranging character of semi-structured interviews also enabled the exploration of additional salient themes. A prominent theme related to feelings of excitement: "I thought it was amazing. . . The outcome definitely has exceeded my expectations. . . Overall the experience has been brilliant" (T2, Participant 1; Table 4.2). For some, excitement was generated by anticipation at the start of the study: "I was quite

excited to do it and I couldn't wait to get to grips with it really" (T2, Participant 6). Excitement also arose with regard to the future potential of diabetes technology, with one woman stating: "I think it's made me look forward to even more what future developments we might have. . . I'm going to end up having just a smartphone app that can control everything" (T2, Participant 11).

Another prominent theme concerned feelings of empowerment arising from participants' feelings of heightened control over their bodies, e.g., "it just makes me think [diabetes is] manageable, it's not as hard as it used to be. . . it can only get better, it can only get easier" (T2, Participant 2). One woman expressed a sense of empowerment in terms of a more equal relationship with clinicians: "Even though I have this . . . disease that's not going to go away, you. . . feel really, well (a) you're in control, because I'm a control freak, I like to be in control of my own health and (b) it's more a partnership, I don't have to sit cap in hand in a waiting room waiting for, you know, two hours for someone to then give me five minutes of time" (T2, Participant 3). Participants rarely experienced these positive views as an immediate or inevitable consequence of closed-loop therapy. Most women (n = 8) expressed initial concerns about automation, remarking for instance that: "I felt like I was giving the control to a device and I found that strange . . . you're handing that control over to a device that initially you don't have any confidence in" (T1, Participant 15).

For some women, experience of closed-loop led to feeling that they had incorporated the system into their body, with diminished perceptions of the system as a signifier of illness. One woman remarked on how she had come to accept the system as "part of her": "[The system] used to be this thing that used to have to hang on my hip or my trousers or be in my pocket. . . And I think it just took a couple of weeks, just seeing the difference it made . . . And as the blood sugars got better and I felt better I was just like, this is just a part of me" (T1, Participant 2).

Table 4.2: Benefits and burdens from qualitative interviews

Category	Themes	Illustrative quotations
Benefit	Improved control	I think it's brilliant because I can come in [on] target …yesterday when I was printing off [the data], I think it was 77% of the time I was on target. T2, Participant 6
	Improved sleep	When you're asleep it is nice to be able to get a full night's sleep knowing that something else is taking control. T2, Participant 1
	Reassurance	I think the best [thing] has been not having to think too much about my blood sugars overnight, you know, having that reassurance that it's doing, hopefully, what it should be doing. T2, Participant 5
	Normality	[B]ecause my blood sugar control is so good and I feel so positive about it it's almost like I'm a normal person and I'm not diabetic. T2, Participant 10
	Empowerment	I don't know what the word is but just...you just feel a little bit at ease that you're not having to worry about something all the time. And even though I like to think that I don't worry I know that

	deep down something like being diabetic is...you do worry about it every day all the time because you don't know when anything's going to happen. I think that was the biggest pro for me is not being, oh I must check my blood sugar, must eat something… can't do this, can't do that. And with this [system] it made me feel well no actually I can. T2, Participant 2
	It was like, it's like being completely blind and then having somebody open your eyes... It puts the power back into your hands because it's all going on inside of you T2, Participant 16
Excitement	[T]he only word I can think of [is] it's quite exciting to know that I can learn something like that and make it work. T2, Participant 2
	I think it's been quite exciting because people ask, what is that, and then I get to explain. I'm quite excited about the study, I really like explaining and people are really curious… My husband's really interested in how well the closed loop works so he's looking at my data and, how did that go, and things. He's been really excited. It's been great that we're both really excited about the study. T2, Participant 11

Burden	Glitches	[P]robably about one in four of the CGM [sensors] has failed… I've had five or six that just wouldn't even connect. T2, Participant 4
	Alarms	Yeah, that's probably been the biggest irritation, yeah, being woken up once or twice a night by alarms. T2, Participant 17
	Trust issues	I don't distrust the doctors, it's the kit… because if anything is going to fail it's the kit. T1, Participant 03
	Lifestyle limits	I am finding it really difficult. I mean, I like to wear things like dresses, and skirts and tops. And it just feels like its protruding out. I don't…I suppose I don't mind putting it on show, but I do find it quite restrictive in what I can wear. T1, Participant 10
		I'm not entirely sure what I'm going to do when I have the baby, because I can see it getting tangled up in it quite a lot… I'm forever waking up and finding me tangled in it, or lying on it. T2, Participant 04
	Obsessiveness	I think the biggest thing is just being able to see your blood sugars in front of you all of the time, and seeing what they're doing. And, it's actually quite scary to begin with… it does come as a little

bit of a shock to the system. Now, I think, if I were to not have the CGM, …you'd miss it, you wouldn't know what to look at. … it's a bit like a smart phone, you know… . T2, Participant 05

I've been a bit obsessed looking at that actually because I was always an avid blood sugar tester anyway, so I'd test eight to ten times a day. So the fact that I haven't had to prick my finger that much and I can literally just pick it up and look at it, so particularly at work if I've been busy I've been managing to just have a look at it. T2, Participant 12

Deskilling

I feel as though my hypo-awareness has dropped, because I think I've become too dependent on [the system] I feel as though, rather than being conscious of how I'm feeling all the time, I'll just wait for the [CGM handheld device] to beep and tell me that I'm going to go low. T2, Participant 14

[O]ne of the negative things is it's made me slightly more passive… it definitely made me lazier and slightly more passive in my own care, which is, I guess, not a good thing. T2, Participant 17

4.4.2 Burdens of closed-loop therapy

Questionnaire data show that participants also experienced burdens arising from closed-loop therapy. Most notably, seven women (67%) reported increased time thinking about diabetes during closed-loop, compared with only three participants (27%) during sensor-augmented pump therapy. This seems to contradict our finding, noted above, that participants saw closed-loop therapy as allowing them "time off" from diabetes; however, it was also noted that participants' remarks in interviews often framed discussion of "time off" in terms of feelings of normality rather than an actual reduction of time spent thinking about diabetes.

Because the closed-loop system requires user input, it is perhaps unsurprising that use of this initially unfamiliar system can lead to a greater amount of time thinking about diabetes. One woman stated: "I think you'd have to have the artificial pancreas for at least a year to feel confident [with it]" (T2, Participant 2).

In addition to increased time thinking about diabetes, eight participants reported that worry about hyperglycaemia was still "very much"/ "quite a lot" of a problem, compared with two during sensor-augmented pump therapy, while three reported that closed-loop made sleep and preventing hyperglycaemia more problematic. There was no association between participants' demographics or baseline HbA1c value and subsequent acceptability of the technology.

Interview data also attested to additional perceived challenges, including device connectivity issues, inaccurate sensor readings (e.g., CGM dropouts from sensor compression during sleep), pump occlusions, unplanned reversion to sensor-augmented pump therapy owing to technical issues, and erroneous low battery readouts (Table 4.2). For some participants, these kinds of problems impacted negatively their trust in the system. As one woman stated: "[The pump] is this thing that's become. . . part of your life and. . . you trust it and. . .it lets you down and it's like, no, you cannot let me down,

I've let you into my life and I trusted you and look what you've done" (T1, Participant 3).

Interviews also revealed women's concern regarding system alarms and their negative impact on sleep, and anxiety arising from the possibility of overnight system failure. As noted, a small number of participants mentioned difficulty sleeping while using the system, mostly as a result of system alarms and glitches rather than anxiety about glycaemic control. As one woman stated: "I've had an awful lot of sleepless nights, with the equipment malfunctioning, just beeping at me all the time, which was quite annoying" (T2, Participant 4; Table 4.2). This woman also went on to note, however, that she was "getting less sleep anyway" because she was pregnant, a theme echoed by a number of other participants. Once again, however, participants learned to deal with these challenges over time: "[T]he first time you have to do it on your own, it's a bit of a struggle. . . you do get used to it, but it was a bit of a.. aargh! for a while. . . you have to watch it just for a while, to make sure it's actually going to work" (T2, Participant 4).

We also identified wider concerns arising from the experience of closed-loop in day-to-day living (Table 4.2). Nine women expressed initial or ongoing device visibility concerns because of the physical bulk of the prototype system (tablet computer, CGM and pump) and the limitations placed on clothing and lifestyle choices. Surprisingly, the questionnaire data showed that only two participants thought the issue of "looking different because of diabetes and using devices" was worse than before the study (Table 4.3). During an interview, one of the women who subsequently discontinued closed-loop stated: "It's not ideal. . . during the winter when you're layered up, its maybe not such an issue, you can hide it easier, but as the weather gets warmer, and you're [wearing] more summery things, it is a little bit restrictive as to what you do with it, where you wear it" (T2, Participant 5).

Table 4.3: Differences between closed-loop insulin delivery and sensor-augmented pump therapy

Benefit or burden	Questionnaire item category	Questionnaire items	Percentage of participants responding in closed-loop insulin therapy (CL) vs baseline	Percentage of participants responding in sensor-augmented pump therapy (SAP)	Difference between CL and SAP (positive value in benefit indicates better experience in closed-loop arm; in burden indicates worse)
Benefit	Not much of a problem/not at all a problem	6. Not knowing how eating affects blood sugar	100	100	0
		12. Pain or discomfort from insulin injections or pumps	100	73	27
		13. Family arguments or worries about diabetes	100	82	18
		11. Pain or discomfort from finger sticks or sensors	84	64	20
		21. Dealing with others who ask about diabetes	84	100	-16
		26. Getting the right amount of insulin on sick days	84	55	29
		27. Feeling that diabetes devices run my life	84	82	2

Mean difference between CL and SAP (positive figure shows better CL experience)				+13
Much better than before study/a little better than before study	3. Worry or fear about low blood sugar during sleep	82	69	13
	2. Effort to keep low blood sugar from happening	73	77	-4
	9. Worry or fear about low blood sugar	55	69	-14
	10. Effort to keep high blood sugar from happening	55	69	-14
	6. Not knowing how eating affects blood sugar	46	62	-16
	18. Knowing how much insulin to take	36	62	-25
	20. Reacting to all the blood sugar results that I get	36	46	-10
Mean difference between CL and SAP (positive figure shows better CL experience)				-10

Burden	Very much a problem/quite a lot a problem	5. Amount of time spent thinking about diabetes	67	27	40
		1. Worry or fear about high blood sugar	50	18	32
		7. Amount of time and effort needed for diabetes from my family or me	33	36	-3
		10. Effort to keep high blood sugar from happening	33	9	24
		14. Trouble sleeping well	33	9	24
		22. My amount of responsibility for taking care of diabetes	33	18	15
	Mean difference between CL and SAP (positive figure shows worse CL experience)				+22

Much worse than before the study/a little worse than before the study	5. Amount of time spent thinking about diabetes	45	23	22
	20. Reacting to all the alarms from diabetes devices	45	39	6
	7. Amount of time needed for diabetes from my family or me	27	23	4
	29. Coping with carrying and using several devices	27	30	-3
	4. Feeling different from others	18	8	10
	20. Reacting to all the blood sugar results that I get	18	15	3
	30. Looking different because of diabetes and using devices	18	25	-7
Mean difference between CL and SAP (positive figure shows worse CL experience)				+5

Prompted by the greatly increased quantity of data that closed-loop provided, some women described obsessive checking of system readouts. They acknowledged that although the system was physically cumbersome it was also an addictive and powerful piece of technology that women interacted with as they would their smartphones: "I wouldn't even be able to tell you how often I [check my levels on the tablet]" (T2, Participant 5). For some, this was a potentially negative phenomenon: "I don't like the whole addiction. . . I was reading about the young mums where they're not getting their actual physical face time with their children. . . because they're texting while they're breastfeeding" (T1, Participant 5); "It would be very easy to get so caught up in it, so absorbed and so fixated" (T1, Participant 3).

Some participants raised the concern that closed-loop therapy diminished their attentiveness to symptoms of hyper- and/or hypoglycaemia, and were concerned about the potential "deskilling" arising from the "outsourcing" of bodily symptoms to system devices: "[W]hen my blood sugars have been. . . starting to decrease, I haven't necessarily felt like I was having a hypo. So maybe that is me, putting all my trust in it, and almost taking my trust out of myself" (T1, Participant 10). The two women who stopped using closed-loop therapy after completing the crossover trial had concerns about battery life, inter-device connectivity and the physical bulk of the system. Both expressed concerns regarding sensor accuracy, leading to a relative lack of trust in the system: "I wouldn't say I trust it massively, [around] 50 or 60%. . . there's always that little doubt in my head. . . there's always glitches that can happen" (T2, Participant 6). Additionally, both found closed-loop insufficiently aggressive in terms of glycaemic control, with one participant stating that she believed there was little difference between closed-loop and sensor-augmented pump therapy: "my control on. . . closed-loop overnight, I didn't find was any better than not being on the closed-loop" (T2, Participant 5).

4.4.3 Potential use of closed-loop in routine clinical care

In terms of potential future mainstream use of closed-loop therapy, a number of women expressed concerns about how the level of 24-hour support offered during a research study would translate into mainstream clinical care. Nine women stated that they would

have considered dropping out without such support. When asked if they would recommend the system to others, most were supportive. Some (n=4) added caveats, suggesting that the system may not be suitable for children, "people with busy practical jobs", "those without motivation to use the system successfully", or those who are "less technologically competent". In this context, one woman stated that: "Personally, I would recommend it to anyone [but] maybe not my granddad who's diabetic because he hasn't really got a clue" (T2, Participant 6).

4.4.4 Perceptions of glucose control

We compared the biomedical data on individual participants' glucose control obtained during overnight closed-loop to quantised qualitative data of women's perceptions of their glucose control (Table 4.4). Women very slightly overestimated their glycaemic response compared with the objectively measured change in glucose control (mean overestimate of 0.1 on a five-point scale). There was marked variation among individuals: two women correctly estimated their glycaemic response, four overestimated their response to closed-loop therapy (mean overestimate of 2.3) and seven underestimated their response (mean underestimate of 1.3).

There was wider variation between women's objectively measured change in glycaemic control (ranging from 2 to 5) than between their perceptions of their response (from 3 to 5).

Table 4.4: Women's views of glucose control in relation to objective glycaemic response and their attitudes to technology

Participant ID	Glycaemic response (1-5)	Opinion of glycaemic response* (1-5)	Disparity: biomedical to interview ^	Attitudes to technology: Baseline (1-5)	Attitudes to technology: Follow-up (1-5)	Change in technology attitudes
1	5	4	-1	3	3	0
2	3	4	+1	2	5	+3
3	5	3	-2	4	3	-1
4	5	4	-1	3	3	0
5	4	3	-1	3	3	0
6	4	3	-1	4	4	0
7	5	5	0	3	4	+1
8	5	5	0	4	4	0
9	5	4	-1	4	5	+1
10	3	5	+2	5	5	0
11	2	5	+3	5	5	0

12	2	5	+3	3	4	+1
13	4	3	-1	2	3	+1
14	4	4	0	n/a	n/a	n/a
Mean	4	4.1	+0.1	3.5	3.9	+0.4

*Women's views of glucose control and attitudes to technology are obtained during qualitative interview and rated on a 1 to 5 scale; entirely positive 5, mostly positive 4, mixed 3, mostly negative 2, entirely negative 1.

The objective glycaemic response as measured by the relative change in overnight CGM time-in-target between CLIP vs self-directed SAP is rated on a 1 to 5 scale; very positive (>15% increase) 5, positive (5-15% increase) 4, neutral (-5 to 5% increase/decrease) 3, negative (-5 to -15% decrease) 2, very negative (<15% decrease) 1.

^Negative values denote that women underestimated their actual glycaemic control; positive values that they overestimated actual glycaemic control

4.4.5 Attitudes to technology

Women's attitudes to technology had a complex and in some ways counterintuitive relationship with their objectively measured change in glucose concentration and with their own perceptions of their glycaemic control (Table 4.5). Overall, women's attitudes towards technology became more positive by 0.4 on a five-point scale over the course of the study; however, seven women showed no change in attitudes towards technology. Of these seven, three correctly estimated their glycaemic control response, while the remaining four underestimated their response (mean underestimatation of 1.25).

Five women showed a positive change in attitudes to technology (mean change 1.4). Of these, two correctly estimated their glycaemic response, two overestimated their response (mean overestimate of 3.5) and one underestimated their response (by 1). One woman, substantially underestimated her glycaemic response to closed-loop therapy (underestimate of 2.0), with a negative change in attitudes (–1), meaning that despite >25% increased time-in-target, she still perceived poor control during closed-loop therapy and was less positive about technology in general. Overall, those who ended the study with the most positive opinion of glucose control and most positive attitudes to technology had poorer levels of glycaemic control and higher degrees of overestimation regarding their levels of control.

Table 4.5: Technology attitudes at baseline and follow up

	Technology attitude	Number (Mean)	Actual CL control (Mean)	Opinion of CL glucose control (Mean)	Disparity between opinion & response (Mean)
Baseline Interview	Entirely negative	0	n/a	n/a	n/a
	Negative	2	3.5	3.5	0
	Mixed	5	4.2	4.2	0
	Mostly positive	4	4.8	3.8	-1
	Entirely positive	2	2.5	5	+2.5
	Mean				+0.7
Follow-up Interview	Entirely negative	0	n/a	n/a	n/a
	Negative	0	n/a	n/a	n/a
	Mixed	5	4.6	3.2	-1.4
	Mostly positive	4	4	4.5	+0.5
	Entirely positive	4	3.3	4.5	+1.2
	Mean				+0.1

4.5 Discussion

The present findings constitute the first insights into the complex psychosocial experiences of women using closed-loop therapy in pregnancy. These women were enrolled in a 2x4 week crossover trial of overnight closed-loop and then had the option of using day-and-night closed-loop for the remainder of their pregnancies. Reflecting the perceived benefits, 14 of 16 women chose to continue using day-and-night closed-loop for up to 12 weeks post-crossover trial.

While our data indicate that closed-loop therapy is, broadly, a positive technological experience, they also show that very positive technology attitudes may be associated with unrealistic expectations. Our key findings relate to the balance between excitement and empowerment alongside concerns about visibility and lifestyle choices, digital addiction, and loss of bodily sensitivity.

These findings have not markedly emerged in previous closed-loop studies, although two studies reported participants' feelings of "hope for the future" and concerns about lifestyle issues (256,257). We also confirm previously reported benefits and burdens of closed-loop therapy over shorter study durations (four weeks), including feelings of "normality" and "time off" from diabetes alongside technical difficulties, alarms, and the physical bulk of the system (256–259).

In terms of perceptions of glucose control, our novel multi-method approach revealed substantial variation in women's estimates of their glycaemic response to closed-loop therapy and the extent to which these aligned (or otherwise) with the objective biomedical data. Our findings suggest that individual users may substantially underestimate or overestimate the control they achieve with closed-loop therapy. We also found that the relationship between attitudes to technology and glucose control was complex and in some ways counterintuitive, because women who ended with more positive perceptions of control and more positive attitudes to technology had comparatively poor glycaemic control. As such, positive attitudes towards technology

may be associated with unrealistic perceptions of glucose control arising from closed-loop therapy.

It is possible that some women's overly positive opinions of control derived in part from pre-existing personal characteristics (e.g. positive attitudes to technology) and satisfaction and excitement generated by trial participation rather than their actual response to therapy. This echoes previous structured education research, in which positive psychosocial outcomes co-existed with limited improvements in glycaemic control (260). Alternatively, participants may have expressed positive views because of experienced benefits not directly related to glucose control, such as improved sleep and "time off" from diabetes.

Conversely, women who underestimated their glycaemic response may have done so because of perceived study burdens and technical glitches, or because of unease arising from obsessiveness or perceived deskilling. The closed-loop system incorporates multiple interconnected devices (insulin pump, CGM device and tablet computer), each of which has its own distinct attributes and "affordances". In particular, participants considered the CGM system both as one of the most beneficial and one of the most burdensome components of closed-loop therapy. The study pump also had specific drawbacks such as manual priming, and was less sophisticated than many commercially available pumps. The tablet was larger and more cumbersome than subsequent iterations which house the algorithm on a mobile phone. In the future, specific device burdens should be reduced as hybrid closed-loop systems become commercially available (187).

The strengths of the present study include our mixed-method approach, which integrated qualitative and quantitative psychosocial data with biomedical data, in addition to our use of a longitudinal rather than cross-sectional approach, which allowed us to examine changes in attitudes over time. In contrast to previous research, which examined intention to use closed-loop therapy, we offered participants a real-life choice to continue using closed-loop therapy during the follow up phase or not.

The study was limited by the small number of participants and the fact that this was the first home study of closed-loop in pregnancy, which may have contributed to women's excitement and positive perceptions.

While future technological progress may obviate specific concerns regarding physical bulk/device visibility issues, other potential challenges such as outsourcing/deskilling and addiction may be more enduring features of automated diabetes technologies. When engaging with optimistic users who risk over-reliance on closed-loop therapy and those who may discontinue use because of negative perceptions of control, clinicians will need to take account of these wider factors to manage expectations and use technology appropriately. Consequently, clinicians should consider closed-loop therapy not just in terms of its potential impact on biomedical outcomes but also in terms of its impact on users' lives. To minimise burdens and maximise benefits, automated insulin delivery systems should consider using co-design approaches to take account of the perspectives of a range of stakeholders, including users and clinicians (261).

4.6 Conclusion

This mixed methods study of pregnant women participating in a trial of closed-loop insulin delivery found that women interacted with and responded to the technology in varied ways. While some participants felt they had improved glucose control while using the technology, these feelings were counterbalanced by concerns about the bulkiness of devices, obsessive data checking and diminished attentiveness to hyper- and hypoglycaemia symptoms.

Participant perception about the impact of closed-loop on their glycaemic control was often discordant with biomedical measures. It is important to recognise that psychological responses to closed-loop therapy in pregnancy can be complex and vary widely between users if we are to understand how this technology might impact women with type 1 diabetes in pregnancy once it becomes commercially available.

5. Closed-loop insulin delivery during labour and delivery

5.1 Background

Achieving optimal glycaemic control throughout pregnancy remains exceptionally demanding for women with type 1 diabetes (227); labour, delivery, and the immediate post-partum period represent unique challenges. Peri-partum maternal hyperglycaemia has frequently, but not always, been associated with a higher risk of neonatal hypoglycaemia (262). Thus, tight glucose control during labour and delivery is generally recommended (22,103,263–265).

Intravenous variable rate insulin infusion (VRII) or continuous subcutaneous insulin infusion (CSII) pumps are the primary methods of insulin therapy used. However, the physiological changes in cortisol, increased glucose utilisation by uterine and skeletal muscles, and the dramatic decrease in insulin resistance immediately after delivery make optimal glycaemic control difficult to achieve in labour, delivery, and the early post-partum period (266). Even with the recommended hourly capillary blood glucose monitoring (22,263), hypo- and hyper-glycaemic excursions are common and frequent insulin dose adjustments are required before and during labour and delivery (267).

Pregnant women with diabetes who are on MDI therapy are generally treated with VRII during labour and delivery. Those on insulin pumps are also often transitioned to VRII

for this period, however, if women are comfortable self-managing their insulin delivery and can maintain their glucose concentration at between 4-7 mmol/L, insulin pump therapy can be safely continued throughout labour and delivery (22,263,267). Self-management using an insulin pump is less invasive and may provide better glycaemic control than VRII during labour and delivery (267).

While some women are comfortable or indeed pleased to have their glucose control managed by staff while in hospital, others report feeling vulnerable when the ability to control their own glucose is taken away from them and is instead 'in the hands' of less experienced delivery ward staff (241). For example, one participant from the overnight closed-loop trial reported in Chapter 2 explained "I don't cope well when you're in a hospital environment and they want to put you on a sliding scale. To me that's like, it's up there with the worst possible diabetes control possible…". Even when women are allowed to continue managing their own insulin delivery, the burden of frequent monitoring and insulin dose adjustments can be stressful during the peri-partum period (268).

Closed-loop insulin delivery uses a continuous glucose monitor (CGM), insulin pump, and computer algorithm to adjust basal insulin delivery. In Chapters 2 and 3 we demonstrated that it could control glucose safely and effectively through the changing demands of pregnancy. Its automated nature and ability to adapt to real-time glucose concentration with minimal user input make it well-suited for use during labour, delivery and the immediate post-partum period.

5.2 Aim

To evaluate the clinical efficacy of closed-loop insulin delivery for maintaining glucose control in women with type 1 diabetes during labour, delivery and the immediate post-partum period.

5.3 Methods

5.3.1 Study participants

This chapter reports on data from participants of the trials described in Chapters 2 and 3. Both trials recruited pregnant women aged 18 to 45 years with at least 12 months duration of type 1 diabetes and HbA1c of 6.5-10% (47.5-85.8 mmol/mol). Women were randomised to receive four weeks of closed-loop insulin delivery (either day-and-night or overnight only) and four weeks of sensor-augmented pump (SAP) therapy, separated by a one to two week washout period. After the randomised trial, women could continue SAP, closed-loop or their preferred intensive insulin therapy. Women who used closed-loop for labour and delivery could continue it until their discharge from hospital during the overnight study or for up to six weeks post-partum in the day-and-night study.

5.3.2 Study design

This was an observational study of all women included in the trials described in Chapters 2 and 3 who chose to use closed-loop insulin delivery during labour, delivery, and the immediate post-partum period.

"Labour" was defined as the 24 hours prior to delivery and "the immediate postpartum period" as the 48 hours after delivery. Glucose control was measured by CGM (FreeStyle Navigator 2, Abbott Diabetes Care, Alameda, CA, USA), insulin delivery was via a DANA-R pump (Diabecare, SOOIL, Seoul, South Korea) and the closed-loop systems used were the FlorenceD2W and Florence D2A (both University of Cambridge, Cambridge, UK). They differed in that the control algorithm was on a tablet PC for the former and on an Android phone for the latter.

The pre-specified glucose control target range during pregnancy was 3.5-7.8 mmol/L and 3.9 to 10 mmol/L after delivery (in line with the non-pregnancy target range,

although participants were advised to aim for glucose levels of 6-10 mmol/L in the early post-partum period). There were no cues or changes in programming to notify the system of labour and/or delivery. Women administered pre-prandial and any additional correction boluses via their insulin pump or the Android mobile phone if they were using the Florence D2A system. Bolus doses were calculated using the standard inbuilt bolus calculator on the DANA-R insulin pump.

The insulin pump settings and carbohydrate ratios were changed as soon as possible after delivery. Women were advised to aim for post-natal glucose targets of 6-10 mmol/L. Participants were instructed not to bolus for their first light meal and only to correct high glucoses concentrations, defined as ≥ 12 mmol/L during the first 48 hours after delivery.

Nursing, midwifery, obstetric, and anaesthetic staff did not receive any formal training with regards to the closed-loop system. However, participants carried with them a simple information sheet that detailed the basic functions of the closed-loop system, listed frequently asked questions, and included the study team contact phone number. Where staff felt unable to deliver optimal care to the participant using the closed-loop system (e.g., in the event of persistent hypo or hyperglycaemia, device malfunction, impaired conscious state, etc.), staff were instructed to disconnect the closed-loop system and use a variable rate intravenous insulin infusion as per standard treatment.

Glucose control was assessed by mode of delivery (vaginal delivery, emergency caesarean section or elective caesarean section). Maternal hypoglycaemic events during intrapartum and post-partum periods were defined as events lasting >20 minutes with a CGM glucose of <3.5 mmol/L and <3.9 mmol/L respectively.

5.3.3 Statistical analysis

Glucose outcomes were calculated with GStat Version 2.2 software (University of Cambridge, Cambridge UK). Statistical analyses were conducted using SPSS and R. The percentage of time-in-target, time hypoglycaemic and time hyperglycaemic were summarised as means (standard deviation) or medians (IQR) where appropriate. Student's t-tests and Mann Whitney Wilcoxon tests were performed as appropriate, and presented with p values and/or 95% confidence intervals. A p value of <0.05 was considered significant.

5.4 Results

5.4.1 Study participants

Of the 32 women enrolled in the two closed-loop trials, 27 (84.4%) continued closed-loop during labour and delivery and their data are included in analyses presented here. They had a mean (SD) age of 32.6 (4.6) years, diabetes duration of 21.9 (8.9) years, booking HbA1c of 7.4 (0.9)% (57.2 [10.3] mmol/mol), and body mass index (BMI) of 28.3 (4.7) kg/m^2.

Table 5.1: Baseline characteristics

Baseline characteristics (N=27)	Number (%)	Mean (SD)
Age (years)		32.6 (4.6)
BMI (kg/m^2)		28.3 (4.7)
Duration of diabetes (years)		21.9 (8.9)
Booking HbA1c		
%		7.4 (0.9)
mmol/mol		57.2 (10.3)
Final HbA1c		
%		6.4 (0.6)
mmol/mol		46.4 (6.4)
Ethnicity		
White	24 (89.0)	
Middle-Eastern	1 (3.7)	
Black African	1 (3.7)	
Mixed ethnicity	1 (3.7)	
Other	0 (0.0)	

5.4.2 Obstetrical outcomes

Measures of glycaemic control during labour and delivery are summarised in Table 5.2, stratified by mode of delivery. The median gestational age at delivery was 37.0 weeks (IQR 34.6, 37.7), with eight pre-term deliveries (29.6%) and 15 (55.6%) large-for-gestational-age infants. There were 18 neonates (66.7%) with hypoglycaemia defined as a glucose concentration of <2.6 mmol/L; of these, 15 infants (56%) were admitted to the neonatal intensive care unit. A further 3 infants were admitted to the neonatal intensive care unit for treatment of sepsis or jaundice but did not have neonatal hypoglycaemia. Six women had pre-eclampsia, three had a post-partum haemorrhage, and one had a urinary tract infection.

Table 5.2: Glucose control during 24 hours prior to delivery, by mode of delivery

	Vaginal Delivery n=4	Emergency Caesarean Section n=12	Elective Caesarian Section n=11
Mean glucose (mmol/L)*	6.3 (0.2)	7.0 (1.5)	7.0 (1.6)
Time in target (%)ᵗ	84.3 (74.7, 88.8)	84.4 (48.5, 93.7)	76.5 (48.2, 93.0)
Time below target (%)ᵗ	0 (0, 3.4)	0.8 (0, 2.0)	0 (0, 2.2)
Time above target (%)ᵗ	15.7 (11.2, 22.0)	11.4 (6.3, 50.4)	16.5 (7.1, 51.8)
Number of hypoglycaemic events (<3.5 mmol/L for ≥20 minutes)ᵗ	0 (0, 1.0)	0 (0, 1.0)	0 (0, 1.0)
Number of women with a hypoglycaemic eventᵗ	1	3	3

Target range is 3.5-7.8 mmol/L.
*Presented as mean (standard deviation)
ᵗPresented as median (interquartile range)

5.4.3 Description of glucose control during labour and delivery and immediately postpartum

Women who used closed-loop during labour and delivery were in the target glucose range 82.0 (IQR 49.3, 93.0)% of time, with a mean glucose concentration of 6.9 (1.4) mmol/L. The time spent above target was 16.0 (IQR 7.1, 46.7)%. Hypoglycaemia was uncommon; median (IQR) 0 (0, 2.2)%. The median (IQR) number of hypoglycaemic events was 0 (0, 1.0), although seven women (26.9%) had at least 1 hypoglycaemic event.

In the first 48 hours post-partum, the mean glucose was 7.2 (1.4) mmol/L. During this period women were in the target range 83.3 (IQR 75.2, 94.6)% of the time, with minimal

hyperglycaemia median (IQR) 9.1 (1.5, 20.6)%. Mild hypoglycaemia was more common post-partum than during labour and delivery; median (IQR) time <3.9 mmol/L was 2.5 (0.9, 5.8)%. The median (IQR) number of hypoglycaemic events was 1.5 (1.0, 3.0), and 21 women (80.8%) had at least one hypoglycaemic event. If a cut-off of <3.5 mmol/L was used, women did not have any hypoglycaemic events in the immediate post-partum period.

There were no incidents of severe hypoglycaemia during labour, delivery, or the immediate postpartum period, nor were there serious device-related adverse events during this time. As expected, the closed-loop system was used with both monopolar and bipolar diathermy without complication.

Table 5.3: Glucose control during labour, delivery and immediately post-partum

	24 hours prior to delivery n=27	**48 hours postpartum n=26**
Mean glucose (mmol/L)*	6.9 (1.4)	7.2 (1.4)
Time in target (%)ᵗ	82.0 (49.3, 93.0)	83.3 (75.2, 94.6)
Time below target (%)ᵗ	0 (0, 2.2)	2.5 (0.9, 5.8)
Time above target (%)ᵗ	16.0 (7.1, 46.7)	9.1 (1.5, 20.6)
Number of hypoglycaemic events (<3.5 mmol/L and <3.9 mmol/L for ≥20 minutes for prior to delivery and postpartum respectively)ᵗ	0 (0, 1.0)	1.5 (1.0, 3.0)
Number of women with a hypoglycaemic event†	7 (26.9)	21 (80.8)

Target range is 3.5-7.8 mmol/L prior to delivery and 3.9-10 mmol/L after delivery
*Presented as mean (standard deviation)
ᵗPresented as median (interquartile range)
†Presented as number (percentage)

5.4.4 Glycaemic control and mode of delivery

The closed-loop system performed well throughout all modes of delivery (vaginal, emergency caesarean section, and elective caesarean section; Table 5.2). Participants used closed-loop insulin delivery under a variety of different methods of anaesthesia including spinal anaesthetic, epidural, and general anesthetic. Additionally, one participant underwent abdominal cystectomy under general anaesthetic following caesarean section under spinal anaesthetic.

5.4.5 Neonatal hypoglycaemia and glucose in labour

There was no difference in mean glucose in mothers of infants with neonatal hypoglycaemia and those without (mean [SD] maternal glucose of 6.9 [1.6] mmol/L and 6.8 [1.1] mmol/L respectively; p=0.84). There was also no difference in the percentage of time in target or time above target (p=0.88 and p=0.76 respectively).

Table 5.4: Glycaemic control in mothers of infants with and without neonatal hypoglycaemia

	Neonatal hypoglycaemia *n* =18	**No neonatal hypoglycaemia *n* = 9**	***p*-value**
Maternal mean glucose in 24 hours prior to delivery (mmol/L)*	6.9 (0.4)	6.8 (0.4)	0.84
Maternal percentage time in target during 24 hours prior to delivery (%)*	73.4 (24.0)	73.1 (21.1)	0.88
Maternal percentage time above target during 24 hours prior to delivery (%)*	25.0 (24.0)	26.0 (21.0)	0.76

Target range is 3.5-7.8 mmol/L
*Presented as mean (standard deviation)

5.5 Discussion

In this cohort, closed-loop insulin delivery performed well during labour and delivery. Women spent over 80% of time within the target range with very little hypoglycaemia in the 24 hours prior to delivery, and only mild hypoglycaemia post-partum (no episodes of glucose <3.5 mmol/L for at least 20 minutes). Closed-loop maintained tight glycaemic control during vaginal deliveries and caesarean sections using regional and general anaesthesia. The system also adapted quickly to the rapid change in insulin requirements immediately after delivery with women spending over 80% of the time in the target range in the immediate post-partum period.

The main limitation of our study is the lack of a standard VRIII or insulin pump control group with which to compare the level of glycaemic control achieved.

The mean glucose achieved using the closed-loop system was comparable to that achieved by other cohorts examining glycaemic control in labour, allowing for differences in definitions and glycaemic targets (109,267,269). Limited data are available when examining time-in-target specifically. Drever et al. (267) assessed time-in-target during labour and delivery in their cohort study of women with type 1 diabetes managed on VRIII or CSII. They found a mean (SD) overall time-in-target of 47.7 (34.9)% compared to our median (IQR) time-in-target of 82.0 (IQR 49.3, 93.0)% however, they had a tighter target range (4.0-6.0 mmol/L) and higher rates of hypoglycaemia (31% of women had at least one episode of hypoglycaemia) than our study. In Drever et al.'s study, insulin pump users who remained on their pump throughout labour and delivery had a lower mean glucose and a trend towards a higher percentage time-in-target than those who transitioned from pump therapy to VRII (5.7 mmol/L vs 6.4 mmol/L, p = 0.02; time-in-target 58.9 vs 39.2%, p = 0.09). However, while these participants were given instructions about insulin dose reduction post-delivery, the authors do not present data regarding early post-partum control, when the insulin doses can be difficult to predict and hypoglycaemia is common. In our study, women spent 83.3% of the first 48 hours after delivery with glucose levels in the target range, with low levels of

hypoglycaemia (2.5% of time below 3.9 mmol/L, no episodes of hypoglycaemia <3.5 mmol/L in any participants).

Closed-loop insulin delivery also offers potential benefits beyond achieving optimal glycaemic control. It may reduce the need to transition from subcutaneous insulin therapy to VRII, which is invasive, limits mobility, and can be distressing to women in labour. VRII also puts a heavier burden on members of the delivery unit staff, who have access to standard delivery protocols but often have limited familiarity with the management of diabetes.

In our studies, all 32 participants were given the choice of using an insulin pump, VRII, or closed-loop therapy during labour and delivery, and 27 of them chose to use closed-loop. Although the qualitative interviews conducted as part of the closed-loop trials did not include specific questions about the use of the system in labour and delivery, a number of participants explained that they were pleased to be able to use the closed-loop system rather than VRII during this period. Comments included "it just took all the worry away, to be honest" (Participant 15, day-and-night trial), "there was me saying to all these doctors, no I'd rather stay on that [the closed-loop system], not the sliding scale…" (Participant 8, overnight trial) and "I was using it even in my labour, my own closed-loop, because it was working fine in making me more relaxed… so I choosed that, rather than choosing the scale, the insulin scale, because I felt more confident with the closed-loop rather than the scale, that's how good it was [sic]" (Participant 11, day-and-night trial). No participants expressed any negative experiences regarding the use of closed-loop therapy during labour and delivery, although it must be noted that participants were not specifically asked about this period during their interviews and that there was no control group with which to compare participants' experiences.

The rapid reduction in insulin requirement post-partum is difficult to predict and highly variable (229), so the closed-loop system might be particularly useful in adjusting insulin doses in the postpartum period. Closed-loop insulin delivery has been demonstrated to be feasible and effective in general and critical care inpatient settings (270,271) and offers

the potential to improve inpatient glycaemic control while reducing the burden on staff, many of whom are not specialised in diabetes management. In a randomised controlled trial of 40 non-pregnant inpatients with type 2 diabetes, a fully closed-loop system was associated with a 22% improvement in the time spent with a glucose concentration within the target range, compared to the routine hospital protocol and was generally well-received by ward staff (270). As people with type 2 diabetes, participants in that study were unfamiliar with CGM or insulin pumps prior to their hospital admission. While comparisons between this study and ours must be cautious given the different patient populations, it does demonstrate the potential for closed-loop to be used for isolated short-term periods when achieving optimal glycaemic control might be particularly difficult, even if the subjects are unfamiliar with diabetes technologies. During pregnancy, these periods might include general antenatal admissions, and admissions for steroid administration, labour, and delivery. It is important, however, to recognise that if this approach were to be adopted, ward staff would need to be trained in the basic use of the closed-loop system and more specialised support staff would need to be available in case of technical difficulties (272).

5.6 Conclusion

This study demonstrates that closed-loop insulin delivery is safe and effective in labour, delivery, and the immediate post-partum period. Women in this study spent more than 80% of the 24 hours prior to delivery with target glucose concentrations and had exceptionally low levels of hypoglycaemia. Closed-loop may be particularly beneficial in the post-partum period when rapid insulin dose reductions are required and hypoglycaemia is common. Our study found that closed-loop could automatically adapt to these changes and achieve very good glycaemic control (83.3% time in target, no episodes of hypoglycaemia <3.5 mmol/L). Future research is needed to compare closed-loop insulin delivery with other modes of insulin delivery during labour and delivery and to assess the use of closed-loop technology in a larger and more diverse population.

6. Neonatal glucose control in offspring of women with type 1 diabetes in pregnancy

6.1 Background

Pregnancies complicated by type 1 diabetes are at increased risk of obstetric and neonatal complications. These include congenital anomaly, macrosomia, pre-term delivery, neonatal hypoglycaemia, and perinatal mortality (1,2,4,58,227,273,274). Even with advances in diabetes care over recent decades, 50% of offspring of women with diabetes are macrosomic, and 40% require admission to neonatal intensive care units (36,47,275). Approximately two in three infants of women with type 1 diabetes have neonatal hypoglycaemia, depending on the definition used (47,68,69). These complications are more common in women with poorer glycaemic control (66,274).

Pregnant women spend approximately a third of the day hyperglycaemic (glucose concentration >7.8 mmol/L) throughout the second and third trimesters (8,144). Maternal glucose is transported across the placenta and transferred to the fetus (276–278). Thus, maternal hyperglycaemia results in fetal beta cell stimulation and hyperinsulinaemia once the fetus begins producing insulin at approximately 16 weeks' gestation (279). After delivery, and therefore the removal of the maternal glucose source, this hyperinsulinaemia can persist and frequently results in neonatal hypoglycaemia. This

theoretical understanding, known as the Pedersen Hypothesis (67), underpins routine clinical advice that women should aim for as near to normoglycaemia as possible throughout pregnancy in order to reduce the transfer of glucose to the fetus and thus reduce the risk of neonatal hypoglycaemia. Indeed, hyperglycaemia at the time of delivery and chronic maternal hyperglycaemia have been associated, respectively, with increased risk and severity of neonatal hypoglycaemia (68). However, this relationship is inconsistently observed (68,267,269,280–283), and the precise relationship between maternal glucose during pregnancy and delivery with neonatal hypoglycaemia remains unclear.

In utero, glucose concentrations are normally maintained between 4-6 mmol/L, but optimal glycaemia in neonates remain undefined and widely debated (284,285). It is often reported that neonatal glucose concentrations fall after birth, reaching a nadir at approximately two hours of life (286). However, more recent studies in healthy term infants suggest that mean glucose concentration remains steady at approximately 3.0 mmol/L during the first two days of life, before gradually increasing to approximately 4.0 mmol/L thereafter (287–289).

Data exploring the relationship between neonatal hypoglycaemia and neurocognitive impairment are limited. While neonatal hypoglycaemia is often asymptomatic, some studies have found it to have long-term consequences including neurocognitive impairment and lower academic achievement (70,290,291). A population-based study of 1395 children found that even transient newborn hypoglycaemia (a single reading below 1.9, 2.2, or 2.5 mmol/L) was associated with lower probability of literacy and mathematics proficiency in fourth-grade tests (291). Additionally, the recent Children With Hypoglycemia and Their Later Development (CHYLD) Study found that, in a cohort of 614 children who had been at risk of neonatal hypoglycaemia, children with CGM-detected neonatal hypoglycaemia had a four-fold increased risk of low executive function 4.5 years of age (292). Those children who had been diagnosed with and treated for hypoglycaemia had were at lower (two-fold increased) risk. However, it is important to note that this cohort was heterogeneous and included infants from 32 weeks' gestation, and those who were small-for-gesational-age or had an acute illness.

While the research suggesting long-term cognitive implications of transient neonatal hypoglycaemia remains preliminary, there is consensus that neonates at risk of hypoglycaemia should be routinely screened and treated if their glucose concentration falls below a pre-determined threshold (variably proposed as 2.0-3.0 mmol/L) (284,285,293).

Continuous glucose monitoring (CGM) has been used successfully to improve glycaemic control and neonatal outcomes for women with type 1 diabetes in pregnancy, with the CONCEPTT trial having described a halving in the odds ratio for neonatal hypoglycaemia requiring intravenous dextrose in women using CGM (150). In infants of women without diabetes, CGM has been used to detect and inform treatment of neonatal hyperglycaemia that is common in pre-term infants, demonstrating that CGM is safe and efficacious even in infants with a very low birthweight (294,295). In a mixed group of infants at risk of hypoglycaemia, CGM was able to detect more episodes of asymptomatic hypoglycaemia than routine heel prick monitoring alone (296).

6.2 Aim

To explore the relationship between maternal glucose control during pregnancy and neonatal hypoglycaemia in pregnancies affected by type 1 diabetes.

6.3 Methods

6.3.1 Study participants

We recruited pregnant women with type 1 diabetes who were in their third trimester of pregnancy. Inclusion criteria included familiarity with continuous glucose monitoring (CGM), intensive insulin therapy using either multiple daily injections of insulin (MDI) or insulin pump therapy, and singleton pregnancy. Exclusion criteria included known congenital anomaly and multiple pregnancy.

6.3.2 Study design

This study was a prospective observational study of pregnant women with type 1 diabetes and their neonatal offspring. Women who were familiar with continuous CGM were approached about the study during their third trimester of pregnancy. Those who wanted to participate in the study provided informed consent for themselves and assent for their infant. Written consent for infant participation was provided by a parent within 24 hours of delivery, prior to any involvement of the infant in the study. Neonates with congenital anomalies or severe respiratory distress were excluded.

The study protocol was approved by the Health Research Authority, East of England Regional Ethics Committee (14/EE/0001).

After recruitment, women had CGM inserted 2-3 days prior to anticipated delivery. Women already using the Guardian REAL-Time or MiniMed Minilink CGM systems (both Medtronic, Northridge, CA) continued on their usual CGM system. Women who were not using one of these systems were fitted with a masked CGM sensor (iPro2 Professional CGM, Medtronic, Northridge, CA, USA). Women were asked to measure blood glucose concentration using their routine glucometer and to record any readings.

As soon as possible following delivery, an appropriately-trained member of the research team fitted a masked CGM sensor (iPro2 Professional CGM, Medtronic, Northridge, CA, USA) onto the infant. The sensors were inserted into the lateral aspect of the neonate's thigh (Figure 6.1). We aimed to fit the CGM sensor to the neonate within 4 hours of delivery. The sensor was left in situ until the infant was suitable for discharge from hospital or for 1 week, whichever was sooner. While infants had the sensor in situ, their routine blood glucose monitoring samples were used to calibrate the CGM. According to the local hospital protocol, infants of women with diabetes have heel prick glucose testing done prior to the infant's second feed and within four hours of delivery. Glucose testing is repeated prior to each feed or every two hours until the infant has had three consecutive values of 2.6 mmol/L or higher. Concurrent sampling was done during these collections for measurement of ketones. Local protocols state that infants should be reviewed by a paediatrician if they are symptomatic, have a glucose value of 1.5 mmol/L, or have more than one reading below 2.6 mmol/L despite breastfeeding. If hypoglycaemia (>1.0 mmol/L but <2.6 mmol/L) persists despite breastfeeding then additional formula feeds or nasogastric feeds can be commenced. If hypoglycaemia persists after one hour, the glucose level is <1.0 mmol/L, or the infant is symptomatic, then an IV dextrose infusion should be commenced.

All infant CGM data were masked and therefore not available to parents, clinicians, or researchers. Infants otherwise received standard clinical care.

Demographics, details of maternal and obstetric history, and circumstances of delivery were obtained from medical notes. Newborn clinical details, including gestational age, birthweight, length, and head circumference, and clinical care requirements were recorded.

Figure 6.1: Continuous glucose sensor attached to the thigh of a newborn infant

6.3.3 Study outcomes

Outcomes assessed included:

- Maternal mean sensor glucose concentration in the 24 hours preceding delivery
- Maternal percentage time with target glucose concentration (3.9-7.8 mmol/L) during the 24 hours preceding delivery
- Lowest recorded newborn blood glucose concentration
- Newborn percentage sensor glucose concentration <2.6 mmol/L within first 48 hours of life
- Newborn percentage time with target glucose concentration (2.6-8.0 mmol/L) first 48 hours of life
- Standard deviation of infant sensor glucose concentration within the first 48 hours of life
- Need for newborn supplemental feeds and intravenous dextrose within the first 48 hours of life

- Need for newborn admission to NICU or special care nursery during the first week of life
- Concentration of ketones measured in newborn blood during first 48 hours after birth

6.3.4 Statistical analysis

Statistical analyses were conducted using R. Where appropriate, student's t-tests, Mann Whitney Wilcoxon tests, linear regression, and analysis of variance (ANOVA) tests were performed and presented with p values and/or 95% confidence intervals. A p value of <0.05 was considered significant.

6.4 Results

6.4.1 Study participants

Twenty two pregnant women with type 1 diabetes were recruited to the study during their third trimester. Of these, 21 participants had maternal and infant continuous glucose monitoring performed (one pair could not be included because there was insufficient CGM equipment available at the time of delivery). In five infants the CGM sensor failed to collect any data, so 16 mother-infant pairs are included in the final analysis. Maternal baseline characteristics are presented in Table 6.1.

Table 6.1: Maternal baseline characteristics

Maternal demographics (N=16)	**Number (%)**	**Mean (SD)**
Age (years)		32.3 (4.3)
Pre-pregnancy BMI (kg/m²)		26.1 (4.1)
		[range 21.0 to 34.8]
Ethnicity (white British)	15 (93.8)	
Duration of diabetes (years)		17.6 (6.8)
		[range 5-31]
Smoker	1 (6.3)	
Current insulin therapy		
- MDI	4 (25)	
- Insulin pump	8 (50)	
- Closed-loop	4 (25)	
HbA1c (mmol/mol / %)		
- Booking		56.9 (8.5)/ 7.4 (0.8)
- 2nd trimester		49.8 (7.8)/ 6.7 (0.7)
- 3rd trimester		50.9 (8.0)/ 6.8 (0.8)

6.4.2 Maternal glycaemic control

Participants had a mean (SD) HbA1c of 56.9 (8.5), 49.8 (7.8), and 50.9 (8.0) mmol/mol in the first, second, and third trimesters respectively (DCCT % units reported in Table 6.1). In the 24 hours prior to delivery, they spent a mean (SD) of 72 (20)% of time (approximately 17.3 hours/day) with target sensor glucose readings (3.9-7.8 mmol/L), 19 (15)% of time (4.6 hours/day) with a glucose concentration greater than 7.8 mmol/L, and 9 (9)% of time (2.2 hours/day) with a glucose concentration below 3.9 mmol/L (Table 6.2). Their mean (SD) glucose in the 24 hours prior to delivery was 6.3 (0.7) mmol/L. There were no statistically significant differences in maternal percentage time in target range or mean glucose in the 24 hours prior to delivery between participants treated with insulin pump (CSII), MDI, or closed-loop therapy (CL) (mean [SD] time in target 66.0 [22.1]% for CSII, 77.0 [20.1]% for MDI, 78.5 [13.4]% for CL, p=0.51; mean [SD] glucose 6.3 [0.9] mmol/L for CSII, 6.2 [0.9] mmol/L for MDI, 6.4 [0.1] mmol/L for CL, p=0.94). However, the study was not designed to compare glucose control with different modes of insulin delivery.

Table 6.2: Maternal glucose control assessed by CGM in the 24 hours prior to delivery, presented by participant

Participant number	Percentage time in target (3.9-7.8 mmol/L)	Percentage time above 7.8 mmol/L	Percentage time below 3.9 mmol/L	Mean glucose (mmol/L)
1	100	0	0	5.2
2	65	26	9	6.8
3	53	40	7	7.0
4	50	50	0	7.7
5	57	12	31	5.3
6	35	40	25	6.7
7	68	15	17	6.8
8	91	0	9	5.1
9	94	3	3	5.4
10	65	20	15	6.3
11	54	31	15	7.0
12	85	15	0	6.3
13	96	4	0	6.0
14	73	16	11	6.0
15	94	6	0	6.6
16	70	24	6	6.4
Mean (SD)	72 (20)	19 (15)	9 (9)	6.3 (0.7)

6.4.3 Obstetric and neonatal outcomes

In this study, women delivered at a mean of 37+2 weeks' gestation (Table 6.3). No women received antenatal steroids prior to delivery. Two women had vaginal deliveries and 14 delivered via caesarean section (9 elective, 5 emergency). Infant birthweight ranged from 2810 to 4675 g (mean [SD] 3887 [519] g). Six infants (37.5%) weighed greater than 4000 g, and two (12.5%) weighed greater than 4500 g.

No infants had congenital anomalies. One required neonatal resuscitation immediately after delivery. All infants were given additional feeds via either expressed breast milk or infant formula. Additionally, 10 infants (62.5%) received treatment with intravenous dextrose. Of the 10 infants who had blood ketones measured, only one had a detectable ketone concentration at any time (0.2 mmol/L), while all other measurements were <0.1 mmol/L.

Table 6.3: Obstetric and neonatal outcomes

Obstetric and neonatal outcomes	**Number (%)**	**Mean (SD)**
Pregnancy-induced hypertension or pre-eclampsia	4 (25.0)	
Mode of delivery		
- Vaginal delivery	2 (12.5)	
- Elective caesarean section	9 (56.3)	
- Emergency caesarean section	5 (31.3)	
Gestation at delivery (weeks)		37.3 (1.1) [range 34+4 to 38+5]
Infant birthweight (g)		3887 (519)
Infant sex		
- Male	10 (62.5)	
- Female	6 (37.5)	
NICU admission	12 (75.0)	
≥1 newborn capillary blood glucose <2.6 mmol/L	15 (93.8)	
Top-up feed given to infant	16 (100.0)	
IV dextrose treatment of infant	10 (62.5)	
Neonatal resuscitation	1 (6.3)	

6.4.4 Neonatal glycaemic control

Fifteen newborns (93.8%) had at least one heel-prick blood glucose reading less than 2.6 mmol/L in the first 24 hours after delivery (Table 6.4). The lowest recorded neonatal blood glucose ranged from 0.7 mmol/L to 3.4 mmol/L for different infants, with a mean (SD) of 1.7 (0.8) mmol/L. Mean (SD) infant sensor glucose was 3.5 (0.8) mmol/L, 3.7 (0.7) mmol/L, and 4.2 (0.6) mmol/L on days 1, 2, and 3 of life respectively.

Infants spent a median (IQR) of 100 (87.3, 100), 100 (99.5, 100.0), and 100 (94, 100)% of the time with sensor glucose readings between 2.6 and 8.0 mmol/L on days 1, 2, and 3 of life respectively.

The percentage time infants spent with sensor glucose readings below 2.6 mmol/L varied substantially between participants, from 0-100% on day 1 of life, 0-57% on day 2 of life, and 0-21% on day 3 of life (median [IQR] for day 1 = 0 [0, 12.8]%, day 2 = 0 [0, 0.5], day 3 = 0 [0, 6.0]). One quarter of infants (n = 4) spent more than 50% of the time with sensor glucose readings below 2.6 mmol/L in their first 24 hours of life. Three of these four infants were not treated with IV dextrose. Two of the three infants who had persistent hypoglycaemia on day 3 of life were not treated with IV dextrose. Two of the infants were documented as being symptomatic of neonatal hypoglycaemia.

Table 6.4: Neonatal glycaemic control by participant

						First 24 hours of life			24 to 48 hours of life		
Participant number	Gestation at delivery (weeks + days)	Birth weight (g)	Admission to NICU	IV dextrose treatment	Lowest recorded blood glucose (mmol/L)	Percentage time with sensor glucose <2.6 mmol/L	Mean glucose (mmol/L)	SD (mmol/L)	Percentage time with sensor glucose <2.6 mmol/L	Mean glucose (mmol/L)	SD (mmol/L)
1	36+1	4490	Yes	Yes	1.0	0	4.3	0.7	0	4.1	0.2
2	37+3	3280	Yes	Yes	1.7	0	3.3	0.3	0	3.2	0.2
3	37+1	4095	Yes	Yes	3.4	0	4.9	0.3	0	5.1	0.5
4	38+3	4280	Yes	Yes	1.9	51	2.6	0.1	57	2.6	0.3
5	37+1	3370	No	No	2.3	0	3.0	0.1	0	3.0	0.1
6	37+0	4675	No	Yes	0.7	0	3.5	0.3	0	4.0	0.7
7	34+4	3815	Yes	Yes	0.9	0	3.7	0.3	0	3.9	0.4
8	38+1	3830	Yes	Yes	2.3	0	4.2	0.3	0	4.2	0.2
9	38+0	2810	No	No	2.2	60	2.6	0.3	46	2.7	0.7
10	37+0	3700	No	No	0.7	54	2.7	0.3	2	3.0	0.5
11	36+4	4035	Yes	Yes	1.0	0	4.8	0.7	0	4.7	0.2

12	38+4	3455	No	No	2.4	0	3.7	0.4	0	3.8	0.5
13	38+0	3880	No	No	1.7	0	3.1	0.1	0	3.4	0.2
14	38+1	3885	No	No	1.7	0	4.1	0.5	0	4.3	0.5
15	37+5	4635	No	No	2.3	100	2.2	0.0	50	3.2	1.3
16	38+5	3990	Yes	Yes	1.1	0	3.4	0.2	0	4.1	0.4

Infants treated with IV dextrose had a mean sensor glucose reading 1.0 mmol/L higher in the first 24 hours of life than those who did not receive treatment with IV dextrose (p = 0.006; Table 6.5). The mean glucose in IV dextrose-treated infants remained significantly higher on day 2 after birth compared with infants who were not treated with IV dextrose (mean [SD] sensor glucose 4.0 [0.7] mmol/L vs 3.2 [0.4] mmol/L, p = 0.03). There were no other differences observed between those infants who did and did not receive IV dextrose. Mothers of infants who were treated with IV dextrose had a lower mean glucose (6.2 mmol/L vs 6.8 mmol/L) and higher percentage time with target glucose levels (89.5% vs 65.0%) although this did not reach statistical significance, perhaps because the study was not powered to assess this difference.

Infants who had at least one blood glucose reading below 1.0 mmol/L were born an average of 1.5 weeks earlier than those whose blood sugar did not drop to 1.0 mmol/L or below (p = 0.01; Table 6.6). There were no other differences in maternal or infant characteristics observed between the infants whose blood sugar did and did not fall below 1.0 mmol/L.

There was no correlation between lowest recorded infant blood glucose concentration and maternal mean glucose concentration, percentage time with target glucose concentration, or percentage time hyperglycaemic (>7.8 mmol/L) in the 24 hours prior to delivery (R^2 = 0.007, p = 0.77 for mean glucose, R^2 = 0.03, p = 0.52 for time in target, R^2 = 0.003, p = 0.85 for time hyperglycaemic). For examples of CGM traces from a selection of mother-infant pairs, see Appendix F.

Table 6.5: Comparison of characteristics for infants treated with IV dextrose compared with infants not treated with IV dextrose

	Infant treated with IV dextrose (*n* = 10)	**Infant not treated with IV dextrose (*n* = 6)**	***p*-value**
Maternal mean glucose in 24 hours prior to delivery (mmol/L)*	6.8 [6.4,7.0]	6.2 [5.6, 6.3]	0.11
Maternal percentage time in target during 24 hours prior to delivery (%)*	65.0 [53.0, 70.0]	89.5 [70.0, 94.0]	0.16
Maternal percentage time hyperglycaemic (>7.8 mmol/L) during 24 hours prior to delivery (%)*	25.0 [15.3, 37.8]	9.0 [4.5, 14.3]	0.12
1st trimester maternal HbA1c (mmol/mol)+	57.3 [9.2]	56.3 [8.1]	0.83
2nd trimester maternal HbA1c (mmol/mol) +	49.6 [7.7]	50.2 [8.6]	0.89
3rd trimester maternal HbA1c (mmol/mol) +	51.1 [9.1]	50.7 [6.9]	0.92
Gestation at delivery (weeks) +	36.9 [1.2]	37.7 [0.6]	0.13
Infant birthweight (g)*	4035 [3830, 4280]	3642 [3391, 3835]	0.14
Lowest recorded infant blood glucose (mmol/L)*	1.4 [1.0, 2.0]	1.9 [1.8, 2.3]	0.31
Infant mean glucose in first 24 hours after birth (mmol/L)+	3.9 [0.7]	2.9 [0.6]	0.006

*Presented as median [IQR]
+Presented as mean [SD]

Table 6.6: Comparison of characteristics for infants who had at least one blood glucose reading below 1.0 mmol/L and those who did not

	Infants with ≥ 1 blood glucose measurement ≤1.0 mmol/L recorded	**Infants who did not have a blood glucose measurement ≤1.0 mmol/L recorded**	***p*-value**
Maternal mean glucose in 24 hours prior to delivery (mmol/L)[*]	6.7 [6.3, 6.8]	6.4 [5.6, 6.8]	0.71
Maternal percentage time with target glucose concentration during 24 hours prior to delivery (%)[*]	65.0 [54.0, 68.0]	77.5 [59.0, 93.3]	0.53
1st trimester maternal HbA1c (mmol/mol)[+]	63.2 [4.3]	53.8 [8.5]	0.12
2nd trimester maternal HbA1c (mmol/mol)[+]	54.2 [4.8]	47.6 [8.2]	0.39
3rd trimester maternal HbA1c (mmol/mol)[+]	53.8 [7.8]	49.5 [8.1]	0.58
Gestation at delivery (weeks)[+]	36.3 [1.0]	37.8 [0.6]	0.01
Infant birthweight (g)[*]	4035 [3815, 4460]	3855 [3391, 4068]	0.31

[*]Presented as median [IQR]
[+]Presented as mean [SD]

6.5 Discussion

In our study population of pregnant women with type 1 diabetes, neonatal hypoglycaemia was near-universal with 15 of 16 infants having at least one recorded blood glucose reading less than 2.6 mmol/L, and all infants receiving top up feeds with either expressed breastmilk or infant formula. Five infants had a blood glucose concentration of ≤1.0 mmol/L recorded at least once.

Continuous glucose monitoring provides much more detailed glucose information than can be obtained via traditional blood glucose testing with a glucometer. This is particularly true for neonates because heel-prick testing is invasive and must be more carefully considered than capillary glucose testing in adults, and because clinically undetected episodes of interstitial hypoglycaemia have been associated with a higher risk of low executive and visual motor functioning at 4.5 years of age (292).

In our study, four infants spent more than half of their first day of life with a glucose concentration of less than 2.6 mmol/L. While blood glucose testing did demonstrate some level of hypoglycaemia in these infants, it was not able to reveal the duration of exposure to hypoglycaemia and three of these four infants were therefore treated only with top up feeds rather than with IV dextrose. These findings are consistent with those of Harris and colleagues (296), who identified that CGM detected much greater exposure to hypoglycaemia than standard blood glucose monitoring in a population of neonates at risk of hypoglycaemia.

In our study, IV dextrose was successfully used to treat neonatal hypoglycaemia with nine of the ten infants who received dextrose subsequently having no hypoglycaemia recorded on CGM. While the mean glucose of 2.9 mmol/L in infants treated with top-up feeds alone was similar to what has previously been described in infants of non-diabetic mothers in the first 24 hours of life (289)), IV dextrose-treated infants had a mean glucose approximately 1 mmol/L higher. Some authors have suggested an association between higher glucose concentrations in the first 48 hours of life and

subsequent neurodevelopmental impairment, especially if episodes were treated with dextrose resulting in a rapid increase in glucose concentrations (297). However, little is known about what represents normoglycaemia in the early neonatal period for offspring of women with type 1 diabetes. It is also difficult to separate the impact of the hypoglycaemia nadir and the post-treatment response as they are highly correlated.

While some previous studies have found neonatal hypoglycaemia to be associated with maternal intrapartum glucose control (68,282,283,298,299), studies of this relationship to date have had discordant results (262), and the pathogenesis of neonatal hypoglycaemia remains poorly understood. Our study was not designed to assess this relationship. However, our results were consistent in direction and suggest that neonatal hypoglycaemia might be more common in women with higher exposure to hyperglycaemia, although this did not reach statistical significance.

A key strength of this study is having detailed glycaemic control information for women and their infants, measured using the same model of CGM sensor. The CGM sensor was inserted into the infant's thigh within four hours of birth, providing novel information regarding glycaemic control in the early neonatal period. Additional strengths include the varied population of women with type 1 diabetes, ranging from those with tight glycaemic control to those with suboptimal glycaemic control. We included women using MDI, insulin pump, and closed-loop therapy, and offered participation to all pregnant women with type 1 diabetes who were familiar with CGM and treated in our centre during the study period. To our knowledge, this is the first study to perform continuous glucose monitoring on women with type 1 diabetes during the intrapartum period and on their infants in the early neonatal period.

However, this study also has a number of limitations. Firstly, the relatively small sample size means that conclusions drawn from the data of this study must be measured. The study is not powered to assess neonatal clinical outcomes or to make comparisons between subgroups of participants. While we aimed to recruit a population of women with type 1 diabetes that was as broad as possible, all of our participants were recruited from a single NHS site with a specialised service for diabetes in pregnancy with higher

than average access to diabetes technologies and full neonatal intensive care facilities. Our participants also had a longer than average duration of type 1 diabetes at conception (227). Therefore our results may not be representative of the wider population of women with type 1 diabetes across the NHS.

Obtaining maximal physiological insights would require studying infants who did not receive any treatment for neonatal hypoglycaemia, which is clearly unethical. In our study, infants received the best available clinical care, which means that our measurements of neonatal glycaemia are affected by treatment with top-up feeds and IV dextrose. These interventions must be used, at least in part as proxies for hypoglycaemia – the full extent of hypoglycaemia that would have occurred with different maternal and infant characteristics cannot be known.

CGM sensors must be inserted manually for neonates to avoid tissue damage or injury from the automated inserting device. This manual insertion is associated with a higher rate of sensor failure. In our study, this meant that five infants had sensors inserted but no data were obtained, necessitating their exclusion from the study.

Further, the CGM system has not been approved for clinical use in neonates and the calibration algorithms are designed for older children and adults who generally have higher glucose concentrations (300). CGM sensor frequently fails to calibrate or record glucose readings if the monitoring is initiated during hypoglycaemia, and CGM is known to be less accurate during periods of hypoglycaemia. The large majority of infants in our cohort had an initial blood glucose reading in the hypoglycaemic range, meaning that the initiation CGM sensor recording was sometimes delayed in our study. This challenge has also been noted by other investigators (296,301) and has the potential to result in an underestimation of exposure to neonatal hypoglycaemia in the first 24 hours after birth.

Although our study has limitations, it provides the most detailed insight into glycaemic patterns in matched mother-infant pairs affected by type 1 diabetes to date. We found a

very high burden of neonatal hypoglycaemia in this cohort, with 15 of the 16 infants having at least one glucose concentration below 2.6 mmol/L recorded, and five infants having at least one reading below 1.0 mmol/L. This is important because even a single reading of this level has been associated with lower achievement test proficiency at 10 years old (291). Further, our study adds to the body of evidence suggesting that CGM can detect hypoglycaemia that goes undetected with routine heel-prick glucose monitoring but has been linked to lower executive functioning at 4.5 years (292). Indeed, a quarter of infants in our study spent at least 50% of the time with a glucose concentration below 2.6 mmol/L. IV dextrose-treated infants had a mean sensor glucose concentration approximately 1 mmol/L higher than the reported average (289) and than the infants in our study who did not receive IV dextrose in the first day of life. This highlights the need for carefully targeted and precise treatment in order to balance potential risks from under- (291,292) or over-treatment (297) of hypoglycaemia.

The relationship between various CGM metrics and long-term clinical outcomes remains poorly understood and results linking transient neonatal hypoglycaemia with longer-term cognitive impairment are still preliminary. Further, the definition of neonatal hypoglycaemia is arbitrary and remains controversial. There is a particular paucity of data related to offspring of women with type 1 diabetes. Long-term follow up studies of larger cohorts would be useful to improve understanding of this relationship. At present, CGM appears to provide useful insights in a research setting, but there is insufficient evidence to support its use in clinical practice. Randomised trials are needed to investigate the impact of real-time CGM in improving glycaemia in the neonatal period. Until then, routine close monitoring of infants at risk of neonatal hypoglycaemia should continue with heel-prick testing in order to optimise clinical outcomes as much as possible.

6.6 Conclusion

Neonatal hypoglycaemia was common in this cohort of infants of women with type 1 diabetes. While most infants in this cohort received treatment with IV dextrose, the full

extent of hypoglycaemia was not appreciated with heel-prick blood glucose monitoring alone. CGM can provide useful insights regarding glycaemia in neonates, but further research is required in order to determine whether there is a role for this technology in the routine clinical care of this population.

7. Conclusions

7.1 Summary of results

7.1.1 Overnight closed-loop insulin delivery in pregnancy

Our randomised trial of overnight closed-loop insulin delivery in pregnancy demonstrated, for the first time, that pregnant women with type 1 diabetes could safely and effectively use this treatment in the home setting. We found that overnight closed-loop was associated with 15% more time spent with a target glucose concentration overnight compared to sensor-augmented pump therapy (74.7% in CL versus 59.5% in SAP; $p = 0.002$). There were low levels of hypoglycaemia during both treatment phases, and no difference in rates of hypoglycaemia or total insulin doses between closed-loop and sensor-augmented pump therapy.

In the follow-up feasibility phase of this study, 14 women elected to continue using closed-loop therapy after their participation in the randomised crossover study for the remainder of their pregnancy. These women achieved excellent glycaemic control (time-in-target 67.6-77.3%) using closed-loop therapy day and night and across a range of normal pregnancy challenges including hospital admissions, antenatal steroid administration, intercurrent infections, labour, and delivery.

7.1.2 Day-and-night closed-loop insulin delivery in pregnancy

After demonstrating the feasibility and efficacy of overnight closed-loop insulin delivery in the home setting for pregnant women with type 1 diabetes, we went on to conduct another randomised crossover trial with a further 16 women, this time looking at the use of closed-loop therapy during both the day and night, when glucose control is more challenging due to meal times and exercise.

In this study, we recruited pregnant women with type 1 diabetes from a wide variety of socioeconomic and educational backgrounds. The cohort as a whole achieved very good levels of glycaemic control during both closed-loop and sensor-augmented pump therapy (time in target 62.3% vs 60.1%, $p = 0.47$). There were no differences in time in target, mean glucose, or time spent hyperglycaemic, but participants had fewer episodes of hypoglycaemia during closed-loop (8 [range 1-17] during closed-loop vs 12.5 [range 1-53] during sensor-augmented pump therapy). They also spent less time hypoglycaemic during closed-loop (1.6% vs 2.7% of the time with glucose <3.5 mmol/L, $p = 0.02$).

In the follow-up phase, all 16 participants elected to continue using day-and-night closed-loop therapy for at least some of the time after their completion of the crossover phase of the study and before delivery. They achieved excellent glycaemic control with 70.6-72.3% of the time spent in the target glucose range (3.5-7.8 mmol/L). After delivery, 12 participants continued using closed-loop therapy for up to 6 weeks post-partum. These participants spent an average of 77.1% of the time in the non-pregnancy target range (3.9-10.0 mmol/L) with very low levels of hypoglycaemia (2.3% of time with glucose concentration <3.9 mmol/L). This trial demonstrated that closed-loop therapy is safe to use continuously in the home setting and that it can effectively control glucose during both the day and night in pregnant women with type 1 diabetes.

7.1.2.1 Comparing the results of the two closed-loop trials

Our trial of overnight closed-loop insulin delivery found that women had lower mean glucose levels and spent 15% more time with target glucose levels overnight during closed-loop therapy than sensor-augmented pump therapy, and this difference persisted across 24 hours. By contrast, our day-and-night trial found that women spent the same amount of time in target and had the same mean glucose during both closed-loop and sensor-augmented pump therapy, but with less exposure to hypoglycaemia.

There are multiple potential explanations for the differences in results observed across the two trials. Firstly, the participants were different. In the day-and-night trial participants were younger, had a shorter duration of diabetes, and had higher booking HbA1cs than participants in the overnight trial (Table 7.1), all factors which may have meant these participants were less experienced with effective diabetes management than those enrolled in the first trial. There were also fewer experienced pump users in the day-and-night trial than in the overnight trial.

Table 7.1: Baseline characteristics in two closed-loop trials

	Overnight trial	**Day-and-night trial**
Age (years)	34.1	32.8
Duration of diabetes (years)	23.6	19.4
Baseline HbA1c (%)	6.8	8.0
Previous pump users (n)	10	8
Weeks' gestation at randomisation	14.0	16.4

Participants in the day-and-night trial also had much more varied lifestyles than those in the overnight trial, which may have made it more difficult for participants to achieve tight glycaemic control. For example, we had one participant who cycled for 60 minutes twice each day, another participant who intermittently worked night shifts (more frequently during her closed-loop phase than during her sensor-augmented pump therapy phase), two participants who travelled abroad for long periods, and three who frequently failed to attend clinic appointments. While our intention was to enroll participants who would comply with the allocated intervention, this had to be balanced against making the trial as pragmatic and "real life" as possible. We did not intend for participants to travel for such extended periods or fail to attend appointments, but were satisfied that these participants were safe given the inbuilt safety mechanisms in the closed-loop systems and the telephone communication we were able to have, so these participants were not withdrawn from the study. Dietary intake, physical activity, and frequency of bolusing substantially impact glycaemic control during closed-loop therapy (238–240), but were not able to be accurately measured in our trials.

The results of our qualitative research presented in Chapter 4 suggest that some participants may have unrealistic expectations of the closed-loop system, and become more passive in their self-management as a result (241). As one participant in the day-and-night trial said during her qualitative interview: "I think if you pay more attention to it, then you're more likely to benefit from it rather than just leaving it to one side and going, oh, that's doing it for me, it's fine" (Participant 11).

Participants in the day-and-night trial had a higher percentage time-in-target and lower mean glucose during sensor-augmented pump therapy than participants in the overnight trial (Table 7.2). The glucose control achieved with sensor-augmented pump in our study was comparable to that achieved with closed-loop in previous studies (173,191), including in well-controlled adults, perhaps leaving less room for improvement (186). In populations of people with well-controlled diabetes, it may be that closed-loop is primarily useful in reducing hypoglycaemia while maintaining tight glycaemic control.

Further, there were a higher number of technical difficulties with the Android mobile phone system (Florence D2A) used in the day-and-night trial than there were with the tablet computer system (Florence D2W) used in the overnight trial. This was largely related to the Bluetooth connection required for the devices to communicate with each other. While most of these technical issues were easily rectified, they did interrupt closed-loop delivery and sometimes required the devices to be reset, deleting the participant-specific adaptations the algorithm had made. In their qualitative interviews, participants of the day-and-night trial explained that these technical issues caused disruption to closed-loop insulin delivery. "You've got three gadgets that are all talking to each other. If the navigator has an issue, then the phone doesn't work, if the phone doesn't work then it just stops. It stops and you just resort back to [sensor-augmented pump therapy]", Participant 11 said. "It quite often comes out with system errors, it's lost communication with the pump, it's system failure or something…you're sitting there, trying to get it to connect, come on, I need to get some insulin in me, " Participant 1 said. While sensor wear was consistently high throughout our trials, we do not have accurate measures of closed-loop usage.

Given the broader population of women included in the day-and-night study, perhaps a period of more than the four weeks was required to become maximally familiar with the closed-loop system. Participant 1 in the day-and-night study explained "I think the four week period to learn the system was too short…I feel like, what I know now, makes me much happier using the system, compared with what I knew when I started using the system."

Indeed, women in both trials who continued to use closed-loop therapy after the crossover part of the study achieved similar levels of glucose control (time-in-target 67.6-77.3% in overnight trial vs 70.6-72.3% in day-and-night trial; Table 7.2). In both trials, participants achieved a higher percentage time-in-target than has been achieved in other published cohorts of women with type 1 diabetes using CGM during pregnancy (145,150), although a lack of control group means comparison between closed-loop therapy and other treatment modalities over the follow up phase is not possible. It is also important to recognise that participants in these trials were supported by a dedicated

research team with access to a 24 hour helpline that may not be available in routine clinical practice.

Table 7.2: Comparison of glycaemic control in two closed-loop trials

		SAP crossover phase	**CL crossover phase***	**28-32 weeks' gestation**	**32-36 weeks' gestation**	**>36 weeks' gestation**
Overnight trial	Time in target (%)	56.8	66.3	67.6	67.8	77.3
	Time below target (%)	1.8	1.9	1.2	1.5	2.1
	Mean glucose (mmol/L)	7.6	7.1	7.1	6.9	6.4
Day and night trial	Time in target (%)	60.1	62.3	70.6	71.5	72.3
	Time below target (%)	2.7	1.6	1.9	2.0	2.3
	Mean glucose (mmol/L)	7.3	7.3	6.9	6.7	6.6

Target range was 3.5-7.8 mmol/L
SAP is sensor-augmented pump therapy, CL is closed-loop insulin delivery
*During the overnight trial, the closed-loop system was used overnight only during the crossover phase, but was used day-and-night in the follow up phase. The glucose measurements presented here refer to the entire 24-hour period.

7.1.3 Experiences of women using closed-loop insulin delivery in pregnancy

While our closed-loop trials demonstrated the feasibility and biomedical efficacy of this technology for pregnant women with type 1 diabetes, understanding the women's experience of using this technology is critical for determining whether or not it will be effective in the wider NHS population.

The participants in the overnight closed-loop trial described in Chapter 2 completed semi-structured qualitative interviews before and after participation in the trial, and questionnaires (the Diabetes Technology Questionnaire and the Hypoglycaemia Fear Survey II) at baseline and following each intervention. These women described the benefits and burdens of using closed-loop systems in pregnancy. While some felt they had improved glucose control while using the technology, these feelings were counterbalanced by concerns about device visibility, obsessive data checking, and diminished attentiveness to hyper- and hypoglycaemia symptoms.

Responding to questionnaires, eight participants felt less worry about overnight hypoglycaemia and that diabetes "did not run their lives" when they were using closed-loop; however, five reported that closed-loop increased time thinking about diabetes, and three felt it made sleep and hyperglycaemia prevention more problematic. Most women became more positive in their technology attitudes throughout pregnancy. When comparing participant perception with biomedical measures, women slightly overestimated their glycaemic response to closed-loop therapy. It is important to recognise that psychological responses to closed-loop therapy in pregnancy can be complex and vary widely among participants, and that perceptions of glycaemic response may be discordant with biomedical data.

7.1.4 Closed-loop therapy during labour and delivery

Women with diabetes in pregnancy are advised to maintain tight glycaemic control during the peri-partum period in order to minimise the risk of neonatal hypoglycaemia.

However, this is difficult to achieve, even with very close glucose monitoring and frequent insulin correction doses. Closed-loop insulin deliveries offers the potential to automatically control glucose during this period.

Therefore, we examined the glycaemic data from the women who used closed-loop therapy during labour, delivery, and early post-partum periods as part of the follow up phase in either of our closed-loop trials. Of the 32 women who participated in our trials, 27 of them used closed-loop during labour and delivery, and 26 used it during the early post-partum phase.

In the 24 hours prior to delivery, women achieved excellent glucose control using the closed-loop system, spending more than 80% of the time with target glucose concentrations (3.5-7.8 mmol/L) with very low levels of hypoglycaemia (median [IQR] 0 [0, 1] episodes). After delivery, insulin requirements fall rapidly and the focus shifts from minimising hyperglycaemia to avoiding hypoglycaemia (target range 3.9-10.0 mmol/L). During this period, women using closed-loop spent more than 80% of the time with target glucose concentrations. Twenty one women (81%) had at least one episode of mild hypoglycaemia (at least 20 minutes with a glucose concentration <3.9 mmol/L), but no participants had any episodes of moderate or severe hypoglycaemia (no episodes of at least 20 minutes with a glucose concentration <3.5 mmol/L).

This study demonstrates that closed-loop insulin delivery can safely and effectively control glucose during the peri-partum period for women with type 1 diabetes. Our study was observational and did not have a control group, so comparisons between closed-loop therapy and other treatment modalities during labour and delivery are not possible from our results. Further studies are warranted in order to determine the relative efficacy, as well as user and staff satisfaction, associated with closed-loop compared with other modes of insulin delivery, including variable rate intravenous insulin infusion and insulin pump therapy.

7.1.5 Neonatal hypoglycaemia in the offspring of women with type 1 diabetes

Neonatal hypoglycaemia has been associated with lower executive functioning at 4.5 years old (292) and lower achievement scores at 10 years old (291), yet remains common in infants of women with diabetes, even when maternal glycaemic control is good. For example, in our closed-loop trials, women had better glucose control than other published cohorts, yet 18 of the 32 infants required treatment for neonatal hypoglycaemia. Patterns of glycaemia in these infants remain poorly understood.

In an attempt to gain insights into neonatal glycaemia in offspring of women with type 1 diabetes, we conducted a prospective observational study of 16 mother-infant pairs. Women were fitted with CGM 2 to 3 days prior to anticipated delivery, and infants were fitted with CGM within four hours of birth.

In this cohort, we found a very high rate of neonatal hypoglycaemia, with 15 of the 16 infants having at least one recorded blood glucose concentration below 2.6 mmol/L. Five infants had a glucose concentration below 1.0 mmol/L and four spent at least 50% of the time hypoglycaemic in their first day of life. This level of dysglycaemia was not identified using heel-prick testing alone.

In their first 24 hours of life, the ten infants who received intravenous dextrose treatment had mean glucose levels approximately 1 mmol/L higher than infants who received top up feeds only and previously reported averages in infants of women without diabetes (289). This is important because a two-year follow-up study found that infants who had higher glucose concentrations in the first 48 hours, particularly when hypoglycaemia had been rapidly corrected with dextrose, faced higher rates of neurological impairment (297).

Our study used CGM to provide novel insights into glycaemic control in offspring of women with type 1 diabetes. Further research is required to determine relationships

between CGM measures and clinical outcomes, and to determine the role for CGM in clinical care.

7.2 Strengths

7.2.1 Closed-loop studies

The closed-loop trials presented in Chapters 2 and 3 had a randomised crossover design that allowed each participant to act as her own control, eliminating confounders (e.g., insulin resistance, variation in dietary habit and physical activity) as much as possible. The only difference between experimental conditions during the period of closed-loop therapy and the period of sensor-augmented pump therapy (SAP) was the therapy being investigated. A crossover design also increases the statistical power of the study, meaning a relatively small sample size can be used, which is particularly beneficial for feasibility studies of new therapies. We used SAP as the comparator because it is the current gold standard in the management of type 1 diabetes in pregnancy. Comparing closed-loop therapy with SAP means that the algorithm itself is being tested, and the results are not confounded by any potential benefit from using insulin pump therapy or continuous glucose monitoring (CGM) alone.

Results were analysed according to intention-to-treat, regardless of compliance with the study protocol. The randomisation for these studies was carried out using an online program to do four-block randomisation. This meant that participants completed the interventions in random order, reducing the impact of a period effect or gestational effect. The four-block randomisation ensured that the groups of participants doing closed-loop or sensor-augmented pump therapy first were balanced, which would have been less likely if simple randomization was used.

Further, while our studies had relatively small sample sizes, we designed them in order for their results to be as broadly applicable as possible. Both studies recruited participants from across three different NHS sites, with different staff experience with diabetes technologies. We recruited participants regardless of their familiarity with insulin pumps and CGM, and our overnight study was the first trial in which participants could be transitioned from multiple daily injections of insulin straight to closed-loop therapy. This is important because it demonstrates that access to this technology does not need to be restricted to those who are experienced with other diabetes technologies and may indeed be beneficial for broad range of people with diabetes.

We recruited women who had a wide range of booking HbA1cs, from 6.5-10%, so as to include as representative sample as possible. In our day-and-night study we broadened our range of participants even further, and included more participants with poorer diabetes control at booking (7 participants with HbA1c >7.5% at booking). Additionally, we included participants who were frequent non-attenders, worked night shifts, and took extended overseas trips without antenatal follow up during those times. We made no restrictions in terms of food or physical activity and continued closed-loop therapy during a range of different normal pregnancy challenges including administration of antenatal steroids for fetal lung maturation, hospital admissions, and labour and delivery under a range of different conditions including induction of labour, elective and emergency caesarean section under regional and general anaesthetic. The system also ran during the early post-partum period where dramatic reductions in insulin requirements make good glycaemic control particularly difficult. No announcements or change in settings were required for the system to cope with any of these challenges. Further, while participants had access to a 24-hour telephone help line if they required technical assistance, we performed no remote monitoring during any part of either trial, so the studies were as "real-life" as possible.

The closed-loop system itself also has a number of strengths. The insulin pump and CGM devices used in our studies were commercially available, so participants could keep this aspect of their care consistent from enrolment in the study until they finished their involvement with the research team. Further, the algorithm we used requires very little

information in order to be initialised. Only the user's weight and total daily dose of insulin are entered into the control algorithm device (tablet computer or mobile phone), with the pre-programmed insulin pump settings transferring automatically from the pump via Bluetooth. Once initialised, the use of the closed-loop system is intuitive and user-friendly. If a similar system became commercially available, it would require minimal additional training for staff familiar with insulin pumps and CGM to be able to train and initiate patients on closed-loop therapy. By nature, the model predictive control algorithm also adapts according to the participant's varying insulin requirements. This is beneficial in terms of providing more glucose-responsive and individualised insulin therapy than can be provided by clinicians relying on retrospective data analysis at appointments in order to adjust future insulin doses. Day-to-day insulin requirements vary substantially, so the relatively fixed basal rates provided certainly by MDI, but also by pump therapy, make it impossible to optimally control blood glucose. This is especially true in pregnancy, where insulin resistance is further influenced by gestational changes in physiology.

The two closed-loop trials presented in this thesis are the first to examine the use of closed-loop therapy in pregnant women in the home setting. The overnight study is also the first study in which participants were transitioned directly from MDI to closed-loop therapy, and the first to use closed-loop during regional and general anaesthetic or administration of glucocorticoids. At the time it was conducted, it was also one of the longest duration studies of closed-loop to date.

Our study of the experiences of pregnant women using closed-loop therapy presented in Chapter 4 provides unique insights that are important prior to considering wider roll out of this therapy. This prospective study used a mixed-methods approach in order to both obtain a detailed understanding of the ways in which participants engaged with closed-loop therapy and also allow us to relate participant perceptions to objective measures of glycaemic control. This is the first study looking at the psychosocial aspects of closed-loop insulin delivery in pregnant women.

7.2.2 Neonatal hypoglycaemia study

The observational study of the relationship between maternal glucose control and neonatal hypoglycaemia also has a number of key strengths. It was a prospective study in which eligible participants were sequentially recruited. We included a broad range of women with diabetes: those using MDI, insulin pumps, and closed-loop therapy and those with poor as well as very good glycaemic control. Some participants had been using CGM in pregnancy and others had not. This was a pragmatic study in which we observed physiology in women and neonates receiving standard clinical care.

This was the first study to examine women with type 1 diabetes in pregnancy together with their neonates using CGM. Using CGM allowed us to obtain detailed information about intrapartum glucose control from the women and glucose control in the first few days of life from the infants. All participants - mothers and babies - used the same model of CGM sensor so results could be directly compared. The sensors were fitted to the infants within four hours of birth, with the aim of capturing glucose control from as early as possible in the neonatal period.

7.3 Limitations

7.3.1 Closed-loop studies

Both our closed-loop trials had relatively small sample sizes. While they were adequately powered to detect changes in the primary efficacy outcome (percentage time with target glucose concentration) based on previous inpatient studies, they were not powered to detect smaller differences in glycaemic control, to conduct sub-group analyses or to assess other outcomes, including obstetric and neonatal complications. However, the crossover design meant that examining the impact of closed-loop therapy on infant outcomes would not have been possible even with larger numbers.

While the randomised crossover design worked well during the overnight study, it was, in hindsight, perhaps less well suited to the day-and-night study given the broader range of participants recruited. Participants had quite varied lifestyles (e.g., intermittent night shifts, overseas trips), which meant that the conditions were different during the two crossover periods, and that the intervention period was not necessarily reflective of the rest of their experience using closed-loop therapy during the remainder of their pregnancy.

We made every effort to include a wide a variety of participants as possible. However, the vast majority of participants were of white British ethnicity, and we only recruited participants who were able to write and speak English. This is reflective of the population of pregnant women with type 1 diabetes at the centres from which we recruited; however this may limit the generalisability of our results.

Further, we approached all eligible pregnant women with type 1 diabetes who attended the recruitment site clinics during our study period, aiming to enrol as broad a range of participants as possible. However, our participants may differ from the broader population of women with type 1 diabetes. People who volunteer to participate in research may be more motivated with regards to their diabetes management than the general population. This should be taken into consideration when designing larger randomised trials, and before closed-loop therapy is included in clinical practice.

Glycaemic control is significantly influenced by carbohydrate intake and physical activity, and we were not able to record these factors during our closed-loop trials.

The closed-loop systems used in our overnight study was a prototype system in which the control algorithm device was a tablet computer. While the system was generally well received by participants, the tablet computer was bulky and limited portability, particularly during the follow-up phase in which participants used the system during both the day and night. The updated system employed for the day-and-night study was more portable, as the control algorithm was housed on an Android mobile phone instead

of on a tablet computer. However, participants were still required to carry an additional device, which – along with the CGM and pump - represented a substantial burden for some participants. Further, the progression to the wireless mobile phone system brought new challenges in terms of connectivity and more frequent technical issues. While most of these could be addressed quickly over the telephone, they were frustrating for participants. Some technical issues required the system to be reset in order to continue closed-loop operation, which meant the algorithm lost the information it had used to adapt the algorithm for the specific individual and had to start again from participant-naïve settings. Ideally, a future commercially available closed-loop system should use one combined interface housed on the insulin pump rather than requiring an additional CGM receiver and a control algorithm device.

Further, we used a hybrid closed-loop system, which required manual pre-prandial boluses that were calculated using the built-in insulin pump bolus calculator and delivered via the pump. Prior to participation in the study, some women had anticipated a fully automated system. Indeed, such systems have been tested in some contexts, but result in poorer post-prandial glucose control due the inherent delays in relying on glucose peaks to be detected in interstitial fluid before insulin is administered. Even with the rapid-acting insulin analogues, the time to peak insulin action is up to 90 to 120 minutes after administration and varies substantially between individuals (205). In pregnancy, these delays, which would in fact be exaggerated as a result of physiological changes in insulin pharmacokinetics, and the resultant prolonged exposure to post-prandial hyperglycaemia would be entirely inappropriate. A future, fully-automated system that could be used in pregnancy would, at minimum, require substantially quicker-acting insulins than are currently available.

During the control phase, women used sensor-augmented pump therapy without a low glucose suspend function. It may be that a low glucose suspend system would offer a reduction in hypoglycaemia compared with regular sensor-augmented pump therapy, although this has not yet been tested in pregnancy. Low glucose suspend systems were not widely used at the time these studies were designed and while they may offer an

appropriate option against which to test the closed-loop algorithm, the sensor-augmented pump therapy we used was more reflective of best available care at the time.

Finally, our studies were supervised by a very small group of specialised clinicians who were able to provide consistent clinical and technical advice to participants. This likely contributed to the high levels of compliance with the technology and the level of glycaemic control achieved. A larger, randomised trial should be conducted across a wider range of NHS centres to examine whether this technology could feasibly be used by and beneficial for women treated by a wider range of staff and in centres with less diabetes technology experience.

7.3.2 Neonatal hypoglycaemia study

The small sample size of our neonatal hypoglycaemia study meant that it was difficult to identify patterns between maternal and infant factors, maternal intrapartum glycaemic control, and neonatal hypoglycaemia. Additionally, there was no control group in this study. Any conclusions drawn in this regard must be regarded with caution.

This was a pragmatic study in which infants were observed during normal clinical care. For this reason, treatment with either top-up feeds or IV dextrose influenced the glucose concentration recorded, and the true nature of the glucose adaptations and the extent of hypoglycaemia that would have been observed in these infants had they not received treatment cannot be known. This limits the physiological insights that can be gained from this study.

Further, the CGM sensors we used are less accurate in the hypoglycaemic range and frequently fail to calibrate or record glucose readings if the monitoring is initiated during hypoglycaemia. The large majority of infants in our cohort had an initial blood glucose reading in the hypoglycaemic range, meaning that the initiation CGM sensor recording

was sometimes delayed, potentially resulting in an underestimation of exposure to neonatal hypoglycaemia in the first 24 hours after birth.

CGM sensors have been used in neonates in research settings but are not approved for clinical use in this population. Calibration algorithms for CGM sensors are designed for children and adults with diabetes, and little is known about the relationship between blood and interstitial glucose in neonates. While the lag between blood and interstitial readings must be considered whenever CGM is used, it is perhaps heightened in the neonatal population (302).

In order to minimise the risk of injury to the neonates, CGM sensor were fitted manually rather than with the automated insertion device generally used for adults. The manual insertion was associated with a higher sensor failure rate than would routinely be expected when the device is inserted as per manufacturer's instructions. In our study, five mother-infant pairs were excluded due to sensor failure in the infant.

Finally, literature regarding the definition of neonatal hypoglycaemia and its potential longer-term impacts remains controversial. Any implications from our findings should be cautious and considered in this context.

7.4 Clinical challenges and future research directions

7.4.1 Closed-loop insulin delivery for pregnant women with diabetes

Together, our overnight and day-and-night studies of closed-loop in pregnancy suggest that closed-loop insulin delivery is safe, feasible, and can effectively control blood glucose for women with type 1 diabetes in pregnancy. However, there are still a number

of challenges to be overcome before this therapy can be rolled out more widely and used in clinical practice.

The most apparent hurdle is the usability of the system. The prototype systems used in the closed-loop studies presented in this thesis had frequent technical issues, which often required trouble-shooting by the research team, and sometimes meant devices needed to be reset or replaced. Additionally, technical faults with closed-loop therapy can have a negative psychological impact (257,303). In our day-and-night study (Chapter 3), 47% of device deficiencies were related to the mobile phone on which the closed-loop algorithm was housed. Some of the technical faults will be resolved with advances in CGM and insulin pump technologies, but ongoing development is required to ensure a system that can feasibly be used in clinical practice without the level of technical support that was required during our studies.

The first hybrid closed-loop device to be commercially released, the MiniMed 670G Insulin Pump System (304), is an integrated system. The closed-loop algorithm is housed on the insulin pump, eliminating the need to carry an additional mobile phone or tablet computer. This is likely to reduce the frequency of connectivity issues and also addresses user concerns about the burden and size of diabetes devices (256,257,303,305).

Post-prandial and exercise-related glycaemic excursions remain significant barriers to achieving optimal glucose control using closed-loop systems (306,307). This is particularly true in fully closed-loop systems, where the effectiveness of dosing in response to meal detection is limited by the pharmacokinetics of insulin, and the delay between ingestion and the subsequent change in interstitial glucose. Hybrid closed-loop systems with manual pre-prandial blousing have performed better to date, and, at present, are the only appropriate option during pregnancy, when glycaemic targets are tighter and the implications of hyperglycaemia are substantial. Perhaps co-administration of pramlinide (308–310) and/or GLP-1 agonists (310,311) with insulin may also help mitigate prandial glycaemic excursions during closed-loop therapy in the future.

Despite continual advances, CGM technology remains a challenge to optimising closed-loop systems. Recent CGM devices have improved accuracy but room for improvement remains (312). The inherent delay between blood and interstitial glucose concentrations makes this difficult to overcome (204,313). CGM systems also require calibration using capillary glucose monitoring, which contributes to the burden of diabetes management. The FreeStyle Libre (Abbott Diabetes Care) flash glucose monitoring system is an alternative that measures glucose continuously but requires users scan a receiver over the sensor before displaying the last eight hours of glucose readings (314). The professional version of it, the Freestyle Libre Pro, is a two-week blinded CGM system (315). Both the Libre and Libre Pro are factory-calibrated and therefore eliminate the need for capillary glucose testing (316), but it is not yet possible to incorporate these sensors into closed-loop systems.

The effectiveness of closed-loop is also limited by the pharmacokinetics of currently available insulins. Even rapid-acting insulin analogues have a substantially slower onset of action and longer duration of action than endogenous insulin (214). In order to avoid hypoglycaemia, closed-loop algorithms must allow for the time to peak insulin activity and the action of insulin that has been delivered but not yet maximally lowered glucose, as well as the duration of action. This necessarily cautious approach can result in periods of hyperglycaemia. Insulin analogues with a quicker onset of action are under development. Fast-acting insulin aspart is the only ultra-fast insulin currently approved and its onset of action and time to peak insulin activity are five to ten minutes quicker than regular insulin aspart (317). While this may allow for some improvement in closed-loop control and could potentially help dampen post-prandial glucose excursions, it is unlikely to dramatically change the parameters that can be safely used in closed-loop algorithms or the glycaemic control that can be achieved for people with type 1 diabetes.

A closed-loop system has already been commercially released (304), but is not yet widely available. At present, it remains unclear who will benefit most from closed-loop therapy. Therefore, patient selection and prioritisation for access to closed-loop will be challenging. In our closed-loop trials (Chapters 2 and 3), pregnant women had variable glycaemic responses to closed-loop therapy, and this did not seem to be related to prior

technology experience, as one might expect. It is not clear from our results to date whether pre-pregnancy planning has an impact on the way women use closed-loop systems or whether commencing closed-loop therapy prior to conception would confer any additional benefit during pregnancy. These issues should be explored in future studies. Our study of experiences of pregnant women using closed-loop (Chapter 4) additionally identified that women interacted with the technology in a wide variety of ways and that their perceptions of the benefits of the system were related to more than glycaemic control alone. It is important that these issues are considered during the roll out of closed-loop therapy. Pregnant women are often excluded from drug and device approval due to insufficient trial data. This is the case with the first commercially available closed-loop system. Given the substantial potential benefit associated with improved glycaemic control for pregnant women with type 1 diabetes, it is critical that randomised trials of new diabetes treatments, including automated insulin delivery systems, are conducted with pregnant women.

Finally, it is important to recognise that, at present, most people with diabetes in the UK, including pregnant women, do not have access to CGM or insulin pump therapy due to limited funding and infrastructure. Most women with type 1 diabetes still enter pregnancy without having achieved the recommended pre-pregnancy targets, and there is substantial inter-centre variability with regards to maternal and infant outcomes (227). Pregnant women with type 1 diabetes should be treated in specialised centres and training programs (including in the use of technology) must be available to all staff involved in the management of these women. As a result of its automated nature, closed-loop insulin delivery has the potential to reduce disparities in outcomes between women of different socioeconomic and educational backgrounds. However, existing strategies, including programs to improve rates of pre-pregnancy care, can also make a substantial difference (2,318–320). Closed-loop is unlikely to be maximally beneficial without good nutrition and general diabetes education.

7.4.2 Next steps in closed-loop in pregnancy research

A large-scale randomised trial of closed-loop therapy that is powered to assess clinical outcomes is required in order to properly understand the impact that this technology is likely to have on a wider population of pregnant women with type 1 diabetes. Given the ongoing limitations with regards to available insulins and technologies, our results suggest that closed-loop therapy is unlikely to radically improve glucose control for women who are already able to achieve near-optimal control using currently available therapies. For women whose glycaemic control is poorer, closed-loop may be a useful management tool to improve glucose control. By automating insulin delivery, closed-loop therapy has the potential to reduce the impact of individual patient factors including education level, socio-economic status, and the level of technology experience of the patient and their care provider. Future research will need to examine whether specific patients are more likely to benefit than others, so that finite resources can be appropriately allocated.

7.4.2.1 Phase III randomised controlled trial

We plan to conduct a large, multi-centre, randomised controlled trial to determine the clinical efficacy of closed-loop insulin delivery in pregnancy. There are a number of important considerations to be made in the design of this trial if it is to provide definitive evidence regarding the impact of closed-loop therapy on pregnancy.

Firstly, the selection of the most appropriate comparator is vital. Sensor-augmented pump therapy is considered the current gold standard for management of type 1 diabetes in pregnancy, and was therefore used as the comparator for the trials presented in this thesis. Indeed sensor-augmented pump therapy with a low glucose suspend feature could be used as a gold standard comparator for a larger randomised controlled trial. However, the majority of pregnant women with type 1 diabetes do not have access to sensor-augmented pump therapy at present, so using it as a comparator would not reflect current clinical practice. By comparing closed-loop to standard care, we can better understand the impact it is likely to have for the vast majority of pregnant women with

type 1 diabetes, if it were to be widely adopted. Given that patient-controlled sensor-augmented pump therapy requires more clinical input than automated closed-loop therapy, and that we demonstrated the feasibility of transitioning participants directly from multiple daily injections (MDI) to closed-loop therapy in our studies, it would potentially be feasible to roll out closed-loop therapy without patient-controlled sensor-augmented pump therapy in some centres. Including technology-naïve participants allows the broadest possible range of participants to be included. For these reasons, it is perhaps most appropriate to assess clinical efficacy of closed-loop by comparing it with standard therapy (237). Further, using standard care as the comparator reduces the cost of the study which will already be considerable.

Secondly, the most appropriate primary outcome is unclear. While the ultimate aim of any intervention for the management of diabetes in pregnancy is to improve outcomes for women and their children, specific clinical outcomes all have significant limitations. For example, the relationship between excess fetal growth, neonatal hypoglycaemia, and maternal glycaemia is not well understood. In the CONCEPTT trial of CGM in pregnancy, infant LGA and neonatal hypoglycaemia rates were halved despite only modest improvements in glycaemic control (150). Other studies have found that infants of women treated with insulin pumps are larger, despite equal (117) or lower maternal HbA1c levels throughout pregnancy (124). HbA1c has been considered an appropriate primary outcome for longer-term diabetes treatment studies outside of pregnancy (175,187,237), but given the limitations of measuring HbA1c in pregnancy, this is less appropriate in this population. Percentage time-in-target as measured by CGM is commonly used as a primary outcome measure in closed-loop studies (185,186,189,321), and is a more appropriate measure of glucose control in pregnancy than HbA1c. This could also be expressed as minutes or hours per day spent within target glucose ranges which may be easier to interpret clinically. Secondary outcomes should include HbA1c, detailed glucose metrics, maternal, obstetric, and neonatal outcomes.

The third major consideration in the design of this trial is its timing. The frequent technical difficulties experienced with the prototype devices would make a larger study with the same devices impractical. It is important to balance the benefit gained from

waiting for inevitable device improvements against delaying a potentially beneficial therapy for women. A hybrid closed-loop system for non-pregnant people with type 1 diabetes was released in 2017 (304); however, this system has not been tested in pregnancy and so cannot be recommended to pregnant women.

In our proposed trial, women with type 1 diabetes will be randomly allocated to either closed-loop insulin delivery or their standard insulin therapy (either MDI or insulin pump) at between eight and 14 weeks' gestation. Since national audit data indicate no difference in glucose control or clinical outcomes between MDI and pump therapy in type 1 diabetes pregnancy (227), we will include both MDI and insulin pump patients in the standard group, stratifying for treatment modality at randomisation.

The primary outcome will be the percentage time with target glucose concentration (3.9-7.8 mmol/L) at 34 weeks' gestation. Based on previous studies of CGM and closed-loop in pregnancy (150,229), we determined that we would need to include 124 participants (62 per arm) in order to detect a 10% absolute difference in the time spent in the target glucose range between closed-loop and standard insulin delivery throughout the day and night. 98 participants are needed to achieve 90% power and an alpha level of 0.05 (two-tailed). The standard deviation of the primary outcome is 15%, as observed in the CONCEPTT trial (150). In order to accommodate an anticipated 10% pregnancy loss before 34 weeks and 10% drop out of randomised participants, we have set a total sample size of 124 participants. We are planning to begin recruitment to the trial in July 2018. Health economics analyses will be conducted as part of the trial in order to determine the cost effectiveness of the intervention. A detailed psychosocial analysis involving study participants and their health professionals will also be conducted.

7.4.2.2 Predicting response to closed-loop insulin delivery in pregnancy

Using the data available from the studies presented in Chapters 2 to 5 of this thesis, we plan to examine predictors of glycaemic response to closed-loop therapy. In the studies conducted to date, the biomedical and psychological responses to the intervention varied

markedly between participants. Given the finite resources available for treating type 1 diabetes in pregnancy, it is important to understand, as much as possible, which patients are likely to respond most favourably to closed-loop therapy. With results of these 32 women, we will investigate the relationships between factors including duration of diabetes, BMI, gestational weight gain, pre-pregnancy and pregnancy HbA1c, gestation at which closed-loop therapy was commenced, experience with diabetes technologies, attitudes to technology, and expectations of closed-loop therapy and the subsequent response to closed-loop therapy. Although the sample size is limited by the number of participants in the two trials, we hope that we can gain useful insights and develop hypotheses that can be tested as part of the larger randomised controlled trial. This study will commence in February 2018.

7.4.3 Understanding infant complications

Risks associated with type 1 diabetes in pregnancy are widely established. Adverse outcomes, including excess fetal growth and neonatal hypoglycaemia, are more common in women with poorer glycaemic control, so the main focus of treatment for diabetes in pregnancy is the optimisation of glycaemic control. However, even with increasing use of new technologies such as insulin pumps and CGM, and concerted efforts to improve glucose control, rates of complications have remained consistently high over recent decades (227).

In our closed-loop study detailed in Chapter 2, glycaemic endpoints showed much tighter glycaemic control than has been achieved in other studies, yet 13 of the 16 infants were still born large-for-gestational-age, and neonatal hypoglycaemia was common. In the study described in Chapter 6, neonatal hypoglycaemia was almost universal. Similarly, a retrospective study of 387 pregnant women with type 1 diabetes (124) found that despite having lower HbA1c measurements throughout pregnancy, women who used insulin pump therapy had higher rates of large-for-gestational-age infants than those who used multiple daily injections of insulin (55.0% vs 39.2% in pump vs MDI groups, $p = 0.007$). In a large cohort of offspring of obese pregnant women, maternal

obesity, late second trimester fasting glucose, gestational weight gain, and antenatal diet were all related to infant adiposity (322,323).

These findings, and recent studies of the maternal metabolome and the cord blood metabolome in women without diabetes (324,325), suggest that excess fetal growth in type 1 diabetes may be related, in part, to factors beyond maternal glycaemic control. However, these other factors remain poorly understood.

A study of maternal metabolites in serum collected from 400 women during an oral glucose tolerance test as part of the Hypogylcaemia and Adverse Pregnancy Outcome Study found an association between fuel metabolites and maternal glucose in pregnancy and found unique metabolites that potentially impact newborn birthweight and adiposity (324).

Additionally, a study of over 700 cord blood samples taken from infants who participated in the German birth cohort study LISAplus found a number of cord blood metabolites that were highly associated with birthweight (325). Together, these results suggest that metabolic factors other than glucose are related to birthweight and that metabolomic analysis of maternal blood and cord blood can provide insights into factors that might predict birthweight and adiposity. Given the high rates of excess fetal growth seen in type 1 diabetes pregnancy, the mechanisms of which are poorly understood at present, further investigation of metabolic factors and their correlation with fetal growth and neonatal adiposity is warranted within the context of type 1 diabetes in pregnancy.

We plan to analyse metabolites in maternal blood of women with type 1 diabetes taken in early and late pregnancy and in cord blood. In our observational study, which will commence in January 2018, we will analyse blood samples that were collected and stored during the CONCEPTT trial of continuous glucose monitoring in pregnancy. We will be able to investigate longitudinal changes in the maternal metabolome across pregnancy in 138 women and assess the relationship between the maternal metabolome and the

cord blood metabolome in the 93 mother-baby pairs for whom we have cord blood samples. We will assess the influence of maternal factors including pre-pregnancy BMI, gestational weight gain, and mode of diabetes treatment (CGM vs SMBG and MDI vs CSII) on the maternal and cord blood metabolome. The results will enable the evaluation of the relationship between the metabolomics data, neonatal adiposity, and neonatal hypoglycaemia parameters. An improved understanding of the physiological mechanisms underlying excess fetal growth and neonatal hypoglycaemia would provide an opportunity for more informed treatment goals and the potential to improve outcomes for women with diabetes and their infants.

7.5 Contribution to knowledge and concluding remarks

Diabetes in pregnancy is the commonest medical condition affecting pregnancy and poses significant risks for mother and baby. While understanding of the pathogenesis of complications remains incomplete, poorer maternal and infant outcomes occur more frequently in women with suboptimal glucose control. However, improving glucose control is difficult owing to day-to-day variation in insulin requirements in people with type 1 diabetes, which is compounded by the changing physiology of pregnancy. Even with targeted efforts and advances in diabetes treatment, including rapid-acting insulin analogues, continuous glucose monitors, and insulin pumps, most pregnant women struggle to achieve optimal glycaemic control.

In this thesis I present the first two home studies of closed-loop insulin delivery in pregnant women with type 1 diabetes. Closed-loop therapy offers a novel management option that may be able to help combat the challenges pregnant women face in improving glucose control by providing personalised, and highly variable insulin delivery automatically in response to real-time glucose concentration measurements. The studies presented in Chapters 2 to 5 of this thesis demonstrate that closed-loop insulin delivery is safe and can effectively control glucose during pregnancy. It appears to offer some benefit when compared to the current gold standard therapy, sensor-augmented pump

therapy. In Chapter 2, the overnight study, we found that closed-loop therapy was associated with participants having a lower mean glucose and higher percentage time with a target glucose concentration during the overnight period. In Chapter 3, the day-and-night study, participants had the same mean glucose and percentage time in target during closed-loop as they did during sensor-augmented pump therapy but had fewer episodes of hypoglycaemia and less exposure to hypoglycaemia during closed-loop therapy.

Closed-loop insulin delivery was generally well received by participants, and almost all women across both studies (30 of 32) elected to continue using it after the crossover part of their study rather than returning to their previous diabetes therapy or to sensor-augmented pump therapy. This prolonged use of closed-loop therapy provided real-life insights and demonstrated that the system was able to control glucose during a range of common pregnancy challenges, including antenatal steroid administration, hospital admissions, labour and delivery under a variety of conditions (presented in Chapter 5), and the first six weeks post-partum. These studies represent the first time that closed-loop therapy has been challenged with these conditions, and the first time it has been used with general anaesthetic, steroid administration, and in insulin pump-naïve patients. Our studies also describe one of the longest durations of closed-loop therapy in any study population to date.

In the first study of women's experiences of using closed-loop insulin delivery in pregnancy (presented in Chapter 4), we found that women had mixed responses to closed-loop therapy, and that their perception of benefit was not necessarily concordant with biomedical outcomes.

Our study of CGM in mother-infant pairs affected by type 1 diabetes provides detailed glucose measurements in a high-risk population. Neonatal hypoglycaemia is very common in the offspring of women with type 1 diabetes but remains poorly understood. We have demonstrated that CGM provides insights beyond heel-prick testing, and

future research will determine whether it has a role in the clinical management of neonatal hypoglycaemia.

There will be some who say that advances in CGM, insulin pump, and closed-loop technology have not yet lived up to the expectations of people with diabetes or health care practitioners. Indeed, the impact of these technologies on maternal glycaemic control during pregnancy appears modest at a population level (Chapter 3, (150)). There will be no single "magic bullet" or revolutionary cure that is appropriate for all women. But anything that helps a majority of pregnant women spend more time with their glucose concentration in the target range and has beneficial health care outcomes for the newborn outcomes should be adopted. Sensor-integrated or automated insulin delivery represents an exciting frontier for type 1 diabetes pregnancy (248), but in the meantime women using injections or pumps with CGM can achieve close to 70% time-in-target range (150). Encouraging women to plan their pregnancies remains an important priority and optimisation of glucose levels prior to pregnancy, using technologies as an adjunct where appropriate, helps improve maternal and infant outcomes. Faster-acting insulins, newer generation CGMs, and future iterations of automated insulin delivery might be needed to minimise postprandial highs and in turn reduce neonatal adverse outcomes even further.

Appendix A: Pittsburgh Sleep Questionnaire

Name:_____ Date: _____

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Appendix B: Daily sleep diary

Please complete the diary each morning that you are wearing your Actiwatch.

Study ID: _____ Start date: _____

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Please enter the day of the week							
What time did you go to bed last night?							
After settling down, how long did it take you to fall asleep (approx.)?							
After falling sleep, roughly how many times did you wake up in the night?							
After falling asleep, for how long were you awake during the night in total?							
At what time did you finally wake up?							
At what time did you get up?							
How would you rate the quality of your sleep last night? 1 2 3 4 5 V. poor V. good							
Times you took off the Actiwatch							

Appendix C: Diabetes Technology Questionnaire

Part 1: Impact and Satisfaction

Thank you for giving us your time and effort in taking part in this study. Your opinions about using diabetes technology are very valuable to us and we hope that you can now help us learn how this has affected your daily life with diabetes. Below you will see some statements about different kinds of diabetes treatments that include using different diabetes devices such as a blood glucose meter, insulin pump, continuous glucose monitor or closed loop insulin delivery system.

Please tick the box below that lists the diabetes devices you are using now as part of treatment. If you aren't sure, ask the diabetes nurse to help you.

☐ Glucose Meter(s) and daily injections of insulin

☐ Glucose Meter(s) and daily use of an insulin pump

☐ Glucose Meter(s) and a Continuous Glucose Sensor (Companion, Navigator, DexCom, Paradigm or Guardian-RT) and daily injections of insulin

☐ Glucose Meter(s) and a Continuous Glucose Sensor (Companion, Navigator, DexCom, Paradigm or Guardian-RT) and daily use of an insulin pump

☐ Glucose Meter(s) and a Continuous Glucose Sensor (Companion, Navigator, DexCom, Paradigm or Guardian-RT) and night-time use of a "closed-loop" insulin delivery system that adjusts insulin doses automatically

☐ Glucose Meter(s) and a Continuous Glucose Sensor (Companion, Navigator, DexCom, Paradigm or Guardian-RT) and 24 hour use of a "closed loop" insulin delivery system that adjusts insulin doses automatically

Now we'd like to ask you some questions about the treatment approach that you selected above. We've listed below some parts of living with diabetes that might be made better or worse by your use of diabetes devices. For each of these, please circle the number that best describes how much of a problem it is now and then circle the number that best describes how it has changed for you **compared to the treatment received before you entered this study.**

Before the study begins, please complete the pink columns only. On all other occasions, please complete the pink and blue columns.

		Is this a problem now?					**How has it changed compared to your treatment before the study?**				
		Very much	**Quite a lot**	**A bit**	**Not much**	**Not at all**	**Much worse**	**A little worse**	**Same**	**A little better**	**Much better**
1.	Worry or fear about high blood sugar	1	2	3	4	5	1	2	3	4	5
2.	Effort to keep low blood sugar from happening	1	2	3	4	5	1	2	3	4	5
3.	Worry or fear about low blood sugar during sleep	1	2	3	4	5	1	2	3	4	5
4.	Feeling different from others	1	2	3	4	5	1	2	3	4	5
5.	Amount of time spent thinking about diabetes	1	2	3	4	5	1	2	3	4	5
6.	Not knowing how eating affects blood sugar	1	2	3	4	5	1	2	3	4	5
7.	Amount of time and effort needed for diabetes from my family or me	1	2	3	4	5	1	2	3	4	5

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very much	Quite a lot	A bit	Not much	Not at all	Much worse	A little worse	Same	A little better	Much better
8. Worry or fear about long term health	1	2	3	4	5	1	2	3	4	5
9. Worry or fear about daytime low blood sugar	1	2	3	4	5	1	2	3	4	5
10. Effort to keep high blood sugar from happening	1	2	3	4	5	1	2	3	4	5
11. Pain or discomfort from finger sticks or sensors	1	2	3	4	5	1	2	3	4	5
12. Pain or discomfort from insulin injections or pump sets	1	2	3	4	5	1	2	3	4	5
13. Family arguments or worries about diabetes	1	2	3	4	5	1	2	3	4	5
14. Trouble sleeping well	1	2	3	4	5	1	2	3	4	5
15. Strictness of the meal plan	1	2	3	4	5	1	2	3	4	5
16. Coping with work or school along with diabetes	1	2	3	4	5	1	2	3	4	5
17. Taking part in sports, exercise, or playing despite diabetes	1	2	3	4	5	1	2	3	4	5
18. Knowing how much insulin to take	1	2	3	4	5	1	2	3	4	5
19. Keeping up with friends or peers who don't have diabetes	1	2	3	4	5	1	2	3	4	5

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very much	Quite a lot	A bit	Not much	Not at all	Much worse	A little worse	Same	A little better	Much better
20. Reacting to all of the blood sugar results that I get	1	2	3	4	5	1	2	3	4	5
21. Dealing with others who ask about diabetes	1	2	3	4	5	1	2	3	4	5
22. My amount of responsibility for taking care of diabetes	1	2	3	4	5	1	2	3	4	5
23. Being sure that pre-meal insulin covers the amount of carbohydrates eaten	1	2	3	4	5	1	2	3	4	5
24. Getting the right amount of insulin when meals are skipped or delayed	1	2	3	4	5	1	2	3	4	5
25. Reacting to all of the alarms from diabetes devices	1	2	3	4	5	1	2	3	4	5
26. Getting the right amount of insulin on sick days	1	2	3	4	5	1	2	3	4	5
27. Feeling that diabetes devices run my life	1	2	3	4	5	1	2	3	4	5
28. Getting the right amount of insulin after exercising more than usual	1	2	3	4	5	1	2	3	4	5
29. Coping with carrying and using several devices	1	2	3	4	5	1	2	3	4	5

	Is this a problem now?					How has it changed compared to your treatment before the study?				
	Very much	Quite a lot	A bit	Not much	Not at all	Much worse	A little worse	Same	A little better	Much better
30. Looking different because of diabetes and using devices	1	2	3	4	5	1	2	3	4	5

Part 2: User Friendliness

Next, we'd like to ask your opinions about the "user-friendliness" of the different diabetes devices that you have been using. For each type of device you have been using, write in the model of the device and then rate that device by circling the number that best matches your opinion about each aspect of using that device.

Blood glucose meter (make/model):						**Other comments about using this blood glucose meter**
	Terrible	**Poor**	**Fair**	**Good**	**Excellent**	
31. Size, weight, appearance and fashion issues	1	2	3	4	5	
32. Ease of start-up, calibration, etc.	1	2	3	4	5	
33. Battery life and ease of replacement	1	2	3	4	5	
34. Variety and flexibility of functions	1	2	3	4	5	
35. Instructions, manual and technical support	1	2	3	4	5	
36. Screen information and reports	1	2	3	4	5	
37. Alarm functions	1	2	3	4	5	
38. Use during sports, exercise, bathing	1	2	3	4	5	
39. Accuracy and reliability of performance	1	2	3	4	5	

Insulin pump (make/model):						Other comments about using this insulin pump
	Terrible	Poor	Fair	Good	Excellent	
40. Size, weight, appearance and fashion issues	1	2	3	4	5	
41. Ease of start-up, calibration, etc.	1	2	3	4	5	
42. Battery life and ease of replacement	1	2	3	4	5	
43. Variety and flexibility of functions	1	2	3	4	5	
44. Instructions, manual and technical support	1	2	3	4	5	
45. Screen information and reports	1	2	3	4	5	
46. Alarm functions	1	2	3	4	5	
47. Use during sports, exercise, bathing	1	2	3	4	5	
48. Accuracy and reliability of performance	1	2	3	4	5	

Continuous glucose monitor (make/model):						Other comments about using this continuous glucose monitor
	Terrible	Poor	Fair	Good	Excellent	
49. Size, weight, appearance and fashion issues	1	2	3	4	5	
50. Ease of start-up, calibration, etc.	1	2	3	4	5	
51. Battery life and ease of replacement	1	2	3	4	5	

Continuous glucose monitor (make/model):						Other comments about using this continuous glucose monitor
	Terrible	Poor	Fair	Good	Excellent	
52. Variety and flexibility of functions	1	2	3	4	5	
53. Instructions, manual and technical support	1	2	3	4	5	
54. Screen information and reports	1	2	3	4	5	
55. Alarm functions	1	2	3	4	5	
56. Use during sports, exercise, bathing	1	2	3	4	5	
57. Accuracy and reliability of performance	1	2	3	4	5	

"Closed-Loop" insulin delivery system:						Other comments about using this "closed-loop insulin delivery system
	Terrible	Poor	Fair	Good	Excellent	
58. Size, weight, appearance and fashion issues	1	2	3	4	5	
59. Ease of start-up, calibration, etc.	1	2	3	4	5	
60. Battery life and ease of replacement	1	2	3	4	5	
61. Variety and flexibility of functions	1	2	3	4	5	
62. Instructions, manual and technical support	1	2	3	4	5	

"Closed-Loop" insulin delivery system:						Other comments about using this "closed-loop insulin delivery system
	Terrible	Poor	Fair	Good	Excellent	
63. Screen information and reports	1	2	3	4	5	
64. Alarm functions	1	2	3	4	5	
65. Use during sports, exercise, bathing	1	2	3	4	5	
66. Accuracy and reliability of performance	1	2	3	4	5	

Appendix D: Hypoglycaemia Fear Survey

This survey is intended to find out more about how low blood sugar makes people feel and behave. Please answer the following questions as frankly as possible.

Behaviour. Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar. Read each item carefully. Circle one of the numbers to the right that best describes what you do during your daily routine to avoid low blood sugar.

	Never	Rarely	Sometimes	Often	Very often
Eat large snacks at bedtime	1	2	3	4	5
Avoid being alone when my sugar is likely to be low	1	2	3	4	5
If test urine, spill a little sugar to be on the safe side. If test blood glucose, run a little high to be on the safe side	1	2	3	4	5
Keep my sugar higher when I will be alone for a while	1	2	3	4	
Eat something as soon as I feel the first signs of low blood sugar	1	2	3	4	5
Reduce my medication when I think my sugar is to low	1	2	3	4	5
Keep my blood sugar higher when I plan to be in a long meeting or party	1	2	3	4	5
Carry fast acting sugar with me.	1	2	3	4	5
Avoid a lot of exercise when I think my sugar is low	1	2	3	4	5
Check sugar often when I plan to be in a long meeting a party	1	2	3	4	5

Worry. Below is a list of concerns people with diabetes sometimes have. Please read carefully. Circle one of the numbers to the right that best describes how often you worry about each item because of low blood sugars.

	Never	Rarely	Sometimes	Often	Very often
Not recognising/realising I am having a reaction	1	2	3	4	5
Not having food, fruit, or juice with me	1	2	3	4	5
Feeling dizzy or passing out in public	1	2	3	4	5
Having a reaction while asleep	1	2	3	4	5
Embarrassing myself or my friends in a social situation	1	2	3	4	5
Having a reaction while alone	1	2	3	4	5
Appearing stupid or drunk	1	2	3	4	5
Losing control	1	2	3	4	5
No one being around to help me during a reaction	1	2	3	4	5
Having a reaction while driving	1	2	3	4	5
Getting a bad evaluation at work because of Something that happens when my sugar is low	1	2	3	4	5
Having seizures or convulsions	1	2	3	4	5
Difficulty thinking clearly when responsible for others (children, elderly, etc)	1	2	3	4	5
Developing long term complications from frequent low blood sugar	1	2	3	4	5
Feeling light-headed or faint	1	2	3	4	5
Having an insulin reaction	1	2	3	4	5

Appendix E: Interview topic guides

To be administered at baseline (T1):

Cognitive frames/attitudes/beliefs

a. Technology/science

- How do you feel about science in general?
    - Are you interested in science?
    - Do you think scientific knowledge is more likely to be true than other beliefs?
- How do you feel about science in healthcare?
    - Is science the best way to treat all health problems?
        - If not, what other approaches do you feel are useful?
- How do you feel about new technologies?
    - How does technology in general, and new technology in particular, feature in your life?
    - Do you see new technology as positive or negative?
    - How do you feel about mobile phones, tablets, laptops, or other forms of portable technology? Do you have any concerns about their use?
- How do you feel about the use of new technologies to monitor activity, behaviour, and other physical characteristics?
    - What could be positive and negative about such use of technology?

b. Diabetes/medicine

- What do you understand by 'quality of life' in a medical context?
    - What impacts do you feel illness has on quality of life?
- What difference does diabetes make to your life?
    - How important is it to you to understand the scientific and technological principles behind treatments for diabetes?
    - How do you see your own role in managing your diabetes?
    - How do you see the role of technology in managing diabetes? Regarding technology in general, but also medical technology?

- What difference does pregnancy make to your attitude towards diabetes? And to technology used to treat diabetes?

c. Artificial pancreas

- Had you heard of the artificial pancreas before signing up for the study?
- What do you expect the artificial pancreas to be like? To look like, feel like?
- What kinds of technology do you think will be involved?
- How do you think it will integrate with your diabetes treatment? Your pregnancy? Your daily life?

To be administered at follow-up (T2):

Outcomes

a. Usability:

- How did you find the process of learning how the technology works?
    - Have you used a CSII pump before?
    - Have you used a CGM monitor before?
        - If yes, did this experience differ from previous experiences? If not, how did it feel to use this technology for the first time?
    - Would you have preferred the tech to be easier to use? If so/if not, why so?
- Regarding the closed loop system, what are your specific thoughts on:
        - Training sessions? Personnel?
            - Did you stay overnight?
        - User manual?
        - CAD (Control Algorithm Device)?
        - Dana-R CSII Insulin pump?
        - CGM Navigator Transmitter and Receiver?
        - Recharging?
        - Sleep/being 'plugged in' overnight?

- Did you make contact with the clinical team? How frequently? Was that helpful?
- Was it easy to remember how to use it?
- Did you make any mistakes using the technology?
- How did you feel about any alarms that may have occurred?
- How good was the technology at fulfilling its purpose(s)?
    - Has it improved your control of diabetes?
    - Did it reduce your fear of hypoglycaemia?

b. Acceptability:

- To what extent were you satisfied with the technology overall?
- How did your experience equate with your expectations before you started the study? Were your expectations fulfilled/challenged/exceeded?
- How easy was it to incorporate into your everyday life?
    - How did it affect your sleep?
    - Did you trust the device?
    - Did you feel you had more or less control over your illness with the device?
    - Would you be comfortable with others seeing the AP/knowing that you were using it? Would it be different with a smaller device?
- Were you concerned about the transmitter being attached to your body/near your child?
    - Would you feel differently if you were not pregnant?
- Might it feel different if you hadn't been using it overnight, while sleeping?
- Did using the technology give rise to any feelings of unease?
    - [Prompt: For example, feelings of being watched or under surveillance? Or feeling that a machine was controlling you?]
- Do you think you would be likely to continue to use it over a longer time period?
    - Which devices did you ask to keep post-study and why?
- Would you recommend its use to others?

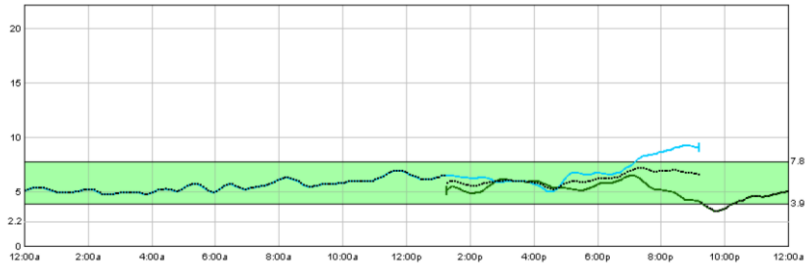
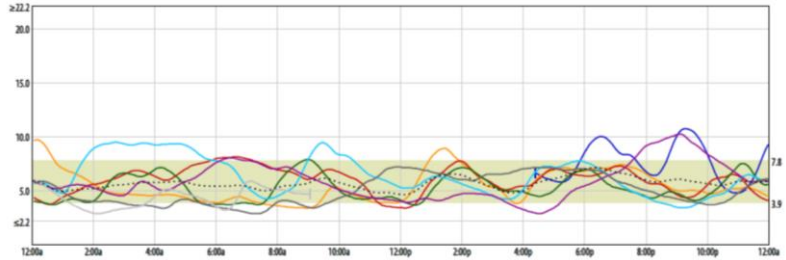
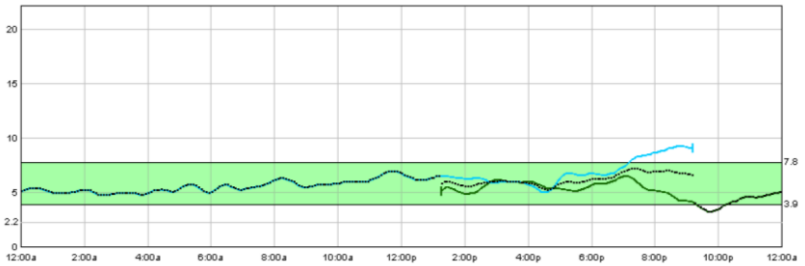
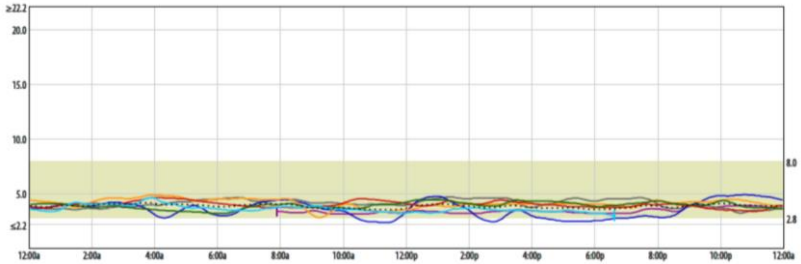
c. Technology

- Has your participation in the study changed your views on:
    - Science
    - Technology
    - New technology
    - Medicine
    - Medical technology and quality of life
    - The role of technology in monitoring/treating illness – and diabetes in particular?
    - Diabetes (and your role in managing your illness)

Appendix F: Examples of CGM traces from mother-infant pairs

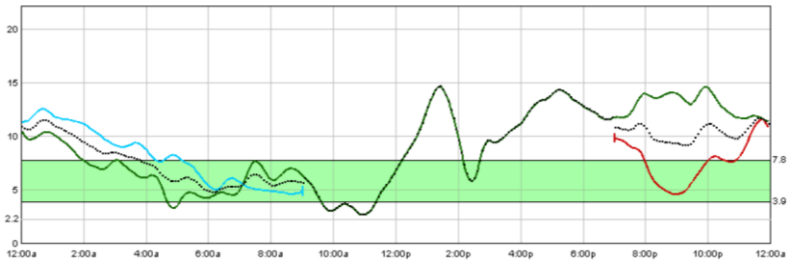
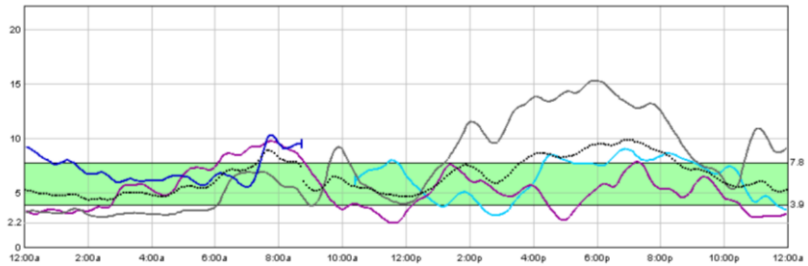
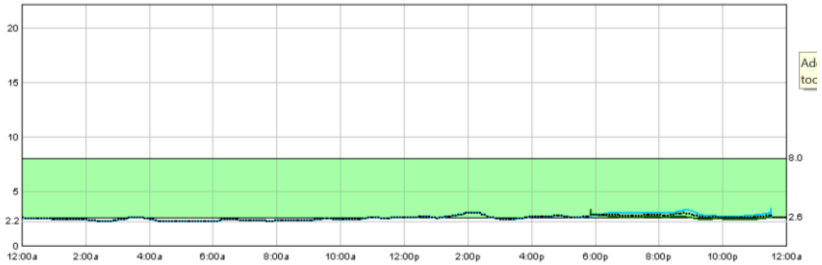
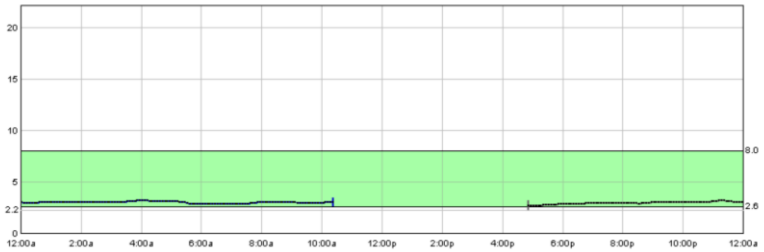
The following pages display CGM sensor traces for a selection of mother-infant pairs. More complete clinical details for each of the participants are available in Tables 6.2 and 6.4.

Mother-infant pairs 8 and 16 had very good maternal glycaemic control, yet both infants required IV dextrose treatment

	Mother-infant pair 8	**Mother-infant pair 16**
	HbA1cs 47, 43, and 47 mmol/mol in trimesters 1, 2, and 3 respectively Mean intrapartum glucose 5.1 mmol/L 91% with target glucose concentration in 24 hours prior to delivery	HbA1cs 43, 34, and 35 mmol/mol in trimesters 1, 2, and 3 respectively Mean intrapartum glucose 6.4 mmol/L 70% with target glucose concentration in 24 hours prior to delivery
Maternal CGM trace		
	Birthweight 3830 g Lowest infant blood glucose concentration 2.3 mmol/L Treated with IV dextrose 0% with glucose concentration <2.6 mmol/L in first 24 hours Mean sensor glucose concentration 4.2 mmol/L in first 24 hours	Birthweight 3990 g Lowest infant blood glucose concentration 1.1 mmol/L Treated with IV dextrose 0% with glucose concentration <2.6 mmol/L in first 24 hours Mean sensor glucose concentration 3.4 mmol/L in first 24 hours
Infant CGM trace		

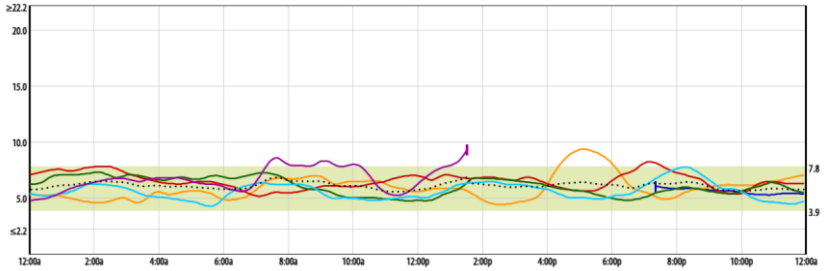
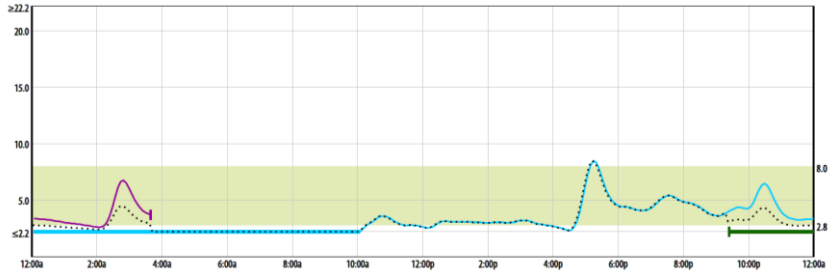
x axis is time of day, y axis is sensor glucose concentration in mmol/L

Mother-infant pairs 4 and 5 had different levels of maternal and subsequent neonatal glycaemic control

	Mother-infant pair 4	**Mother-infant pair 5**
Maternal CGM trace	HbA1cs 64, 50, and 48 mmol/mol in trimesters 1, 2, and 3 respectively Mean intrapartum glucose 7.7 mmol/L 50% with target glucose concentration in 24 hours prior to delivery 	HbA1cs 51, 40, and 41 mmol/mol in trimesters 1, 2, and 3 respectively Mean intrapartum glucose 5.3 mmol/L 57% with target glucose concentration in 24 hours prior to delivery 
Infant CGM trace	Birthweight 4280 g Lowest infant blood glucose concentration 1.9 mmol/L Treated with IV dextrose 51% with glucose concentration <2.6 mmol/L in first 24 hours Mean sensor glucose concentration 2.6 mmol/L in first 24 hours 	Birthweight 3370 g Lowest infant blood glucose concentration 2.3 mmol/L Not treated with IV dextrose 0% with glucose concentration <2.6 mmol/L in first 24 hours Mean sensor glucose concentration 3.0 mmol/L in first 24 hours 

x axis is time of day, y axis is sensor glucose concentration in mmol/L

Mother-infant pair 15 had moderately good maternal glycaemic control during pregnancy, exceptional intrapartum glycaemic control but extensive neonatal hypoglycaemia

	Mother-infant pair 15
Maternal CGM trace	HbA1cs 58, 54, and 52 mmol/mol in trimesters 1, 2, and 3 respectively Mean intrapartum glucose 6.6 mmol/L 94% with target glucose concentration in 24 hours prior to delivery 
Infant CGM trace	Birthweight 4635 g Lowest infant blood glucose concentration 2.3 mmol/L Not treated with IV dextrose 100% with glucose concentration <2.6 mmol/L in first 24 hours Mean sensor glucose concentration 2.2 mmol/L in first 24 hours 

x axis is time of day, y axis is sensor glucose concentration in mmol/L

Appendix G: Achievements

Original research publications

- **Stewart ZA**, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, Simmons D, Law GR, Scott EM, Hovorka R, Murphy HR. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. *New England Journal of Medicine*. 2016; 375:644-654

- Farrington C, **Stewart ZA**, Barnard K, Hovorka R, Murphy HR. Experiences of closed-loop insulin delivery among pregnant women with Type 1 diabetes. *Diabetic Medicine*. 2017; 34, 1461-1469.

- Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, Asztalos E, Barrett JFR, Sanchez JJ, de Leiva A, Hod M, Jovanovic L, Keely E, McManus R, Hutton EK, Meek CL, **Stewart ZA**, Wysocki T, O'Brien R, Ruedy K, Kollman C, Tomlinson G, Murphy HR, on behalf of the CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicenter international randomised controlled trial. *Lancet*. 2017; 390(10110): 2347-2359

- Tauschmann M, Allen JM, Wilinska ME, Thabit H, **Stewart Z**, Cheng P, Kollman C, Acerini CL, Dunger DB, Hovorka R. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: a free-living, randomized clinical trial. *Diabetes Care*. 2016; 39(7): 1168-1174

Planned publications

- **Stewart ZA,** Wilisnka ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, Barnard K, Farrington C, Hovorka R, Murphy HR. Day-and-night closed-loop in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. Manuscript submitted.

- **Stewart ZA**[*]**,** Yamamoto J[*], Wilinska ME, Hartnell S, Hovorka R, Murphy HR. Adaptability of closed-loop during labor, delivery and postpartum: a secondary analysis of data from two randomized crossover trials in type 1 diabetes pregnancy. [*]Joint first authors. Manuscript in preparation.

- **Stewart ZA,** Murphy HR, Thomson L, Beardsall K. Neonatal glucose control in offspring of women with type 1 diabetes in pregnancy. Manuscript in preparation.

Published abstracts

- Neoh S, Grisoni J, **Stewart ZA**, Feig DS, Murphy HR. The CONCEPTT-Diet study: an analysis of diet and glycaemia in UK women with type 1 diabetes before and during pregnancy. *Diabetologia*. 2017; 60 S436-S436

- **Stewart ZA**, Wilinska ME, Hartnell S, Simmons D, Temple R, Stanley K, Rayman G, Hovorka R, Murphy HR. Closed-loop insulin delivery in the intrapartum and early postpartum period in women with type 1 diabetes in pregnancy. *Diabetes*. 2016; 65: A353-A353

- **Stewart ZA**, Wilinska M, Hartnell S, Simmons D, Temple R, Stanley K, Rayman G, Hovorka R, Murphy HR. Overnight closed-loop insulin delivery at home in pregnant women with type 1 diabetes: a feasibility study. *Diabetic Medicine.* 2016; 33: 13

- Murphy HR, **Stewart Z**. Who needs an artificial pancreas in pregnancy? *Diabetes Technology & Therapeutics.* 2016; 18: A14-A14

- Murphy HR, **Stewart Z**, Hovorka R. Revolutionalising type 1 diabetes metabolic control in pregnancy. *Bioscientifica.* 2015; 38.

Review papers & book chapters

- **Stewart ZA,** Murphy HR. To pump or not to pump in pregnancy? *Diabetes Technology & Therapeutics.* 2017; 19(5): 269-270

- Piper L, **Stewart ZA**, Murphy HR. Gestational diabetes. *Obstetrics, gynaecology and reproductive medicine*. 2017; 27(6): 171-176

- Hadar E, **Stewart ZA,** Hod M, Murphy HR. Technology and pregnancy. *Diabetes Technology & Therapeutics.* 2017;19(S1): S-28-S-93.

- Canciani G, **Stewart ZA**, Murphy HR. Advances in insulin therapy. *A practical manual of diabetes in pregnancy.* 2nd edition. Wiley Publishers. 2017

- Murphy HR, **Stewart ZA**. Automated insulin delivery: what's new, needed, and next? *Lancet*. 2017; 389 (10067): 333-334

- **Stewart ZA** and Murphy HR. Closed-loop in Type 1 diabetes pregnancy. *Textbook of diabetes and pregnancy.* 3rd edition. CRC Press. 2016

- **Stewart ZA** and Murphy HR. Gestational diabetes. *Medicine.* 2014; 43(1):44-47

Awards

- Gates Cambridge PhD Scholarship, 2014-2017
- Jean Hailes for Women's Health Australia Fellowship for Emerging Leaders in Women's Health, 2014-2017
- Young Investigators Travel Grant, International Society of Obstetric Medicine Congress, 2017
- Abstract selected for UK Young Diabetologist and Endocrinologist Forum Award Session, Diabetes UK Annual Conference, 2016
- Young Investigators Award, EASD Diabetes Pregnancy Study Group Meeting, 2015
- Chibnall Travel Fund Bursary, Clare College, University of Cambridge, 2015

Presentations

Invited presentations

- "Optimizing glycemic control in pregnancy: insulin pumps, continuous glucose monitors, and closed-loop systems", Charles H Best Diabetes Centre Annual Conference, Toronto Canada, 2017

- "Closed-loop systems in type 1 diabetes pregnancy", UK National Diabetes in Pregnancy Conference, London UK, 2016

- "Type 1 diabetes pregnancy: pumps, monitors and closed-loop systems", MacDonald Obstetric Medicine Society Annual Conference, Oxford UK, 2016

- "Gestational diabetes, diabetes, and pregnancy", National Center for Diabetes Endocrinology and Genetics Diabetes Educational Congress, Amman Jordan, 2016

- "New concepts in diabetes", East Anglian Association of Anaesthetists Core Topics and Harold Youngman Prize Meeting, Newmarket UK, 2015

- Panel member. "The curious museum of medical devices", Theorising Personal Medical Devices Symposium, Cambridge UK, 2014

Abstract presentations

- **Stewart ZA,** Hartnell S, Simmons D, Temple R, Stanley K, Wilinska M, Hovorka R, Murphy HR. Overnight closed-loop insulin delivery at home in pregnant women with type 1 diabetes. [oral] Diabetes UK Professional Conference, Glasgow UK, 2016.

- **Stewart ZA**, Wilinska ME, Hartnell S, Simmons D, Temple R, Stanley K, Hovorka R, and Murphy HR. Closed-loop insulin delivery in the intrapartum and early postpartum period in women with type 1 diabetes in pregnancy. [moderated poster] American Diabetes Association 76th Scientific Sessions, Boston USA, 2016

- **Stewart ZA**, Hartnell S, Simmons D, Temple R, Stanley K, Wilinska M, Hovorka R, Murphy HR. Overnight closed-loop insulin delivery at home in pregnant women with type 1 diabetes: a feasibility study. [oral] EASD Diabetes Pregnancy Study Group Meeting, Malaga Spain 2015.

- Tauschmann M, Allen JM, Wilinska ME, Thabit H, **Stewart ZA,** et al. Day and night closed loop insulin delivery in young people with type 1 diabetes: a free-living, randomised clinical trial. American Diabetes Association 75th Scientific Sessions, 2015.

- **Stewart ZA,** Thomson L, Murphy HR, Beardsall K. Associations between maternal glucose control in pregnancy and neonatal glucose control in offspring of women with type 1 diabetes. [poster] International Diabetes in Pregnancy Symposium: Diabetes, hypertension, metabolic syndrome & pregnancy, Berlin Germany, 2015

- **Stewart ZA,** Grisoni J, Stubbington K, Harding R, Byrne C, Murphy HR. Type 1 diabetes in pregnancy complicated by severe gastroparesis. [poster] UK National Diabetes in Pregnancy Conference, Newcastle UK, 2014

- **Stewart ZA,** Goudie RJB, Lunn D, Hovorka R, Murphy HR. Pharmacokinetics of insulin aspart in pregnant women with type 1 diabetes: Every day is different. [poster] EASD Diabetes Pregnancy Study Group Meeting, Budapest Hungary, 2014.

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