What's new in the management of type 1 diabetes in pregnancy?

Abstract

Type 1 diabetes in pregnancy is associated with an increased risk of complications for both mother and fetus. However, managing glycaemia during pregnancy to reduce these risks is challenging, owing to changes in insulin resistance with advancing gestation, as well as increased daily variation in insulin pharmacokinetics. These factors can add significant psychological and daily self-care burden to mothers during what may already be an anxious time. Increasingly, diabetes technologies are being used during pregnancy to improve and facilitate diabetes self-care. While these can be empowering for people with type 1 diabetes, careful consideration is required in relation to how and when these can be continued safely in the inpatient setting (including acute antenatal admissions, labour and delivery) and when extra support is required from adequately trained healthcare professionals. This article describes current forms of diabetes technologies used and the latest national guidance relating to the care of type 1 diabetes in pregnancy.

Key words: Antenatal hospital admissions; Closed-loop; Continuous glucose monitoring; Diabetic ketoacidosis; Diabetes technology; Pregnancy; Type 1 diabetes

Submitted: 15 September 2022; accepted following double-blind peer review: 1 November 2022

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Introduction

In the UK, 5% of pregnant women are affected by diabetes mellitus every year. Of that 5%, 7.5% have type 1 diabetes, the prevalence of which has been increasing over the last 20 years. During pregnancy, type 1 diabetes is associated with increased risk of complications for both mother and fetus. Risks to the mother include increased rates of severe hypoglycaemia, diabetic ketoacidosis and potential worsening of diabetes microvascular complications, alongside increased risks of obstetric complications, such as preeclampsia, and serious adverse pregnancy outcomes (congenital anomaly, stillbirth and neonatal death). One in two pregnancies are complicated by preterm birth, large for gestational age babies, neonatal respiratory distress, hyperbilirubinaemia, hypoglycaemia and/or admission to the neonatal care unit (Evers et al, 2004; Murphy et al, 2021).

It is well established that optimal maternal glycaemia before and during pregnancy can reduce the risk of complications (Evers et al, 2004; Maresh et al, 2015; Murphy et al, 2021). However, achieving and maintaining target glucose levels throughout pregnancy is challenging, owing to gestational variations in insulin resistance and increased daily variability in insulin pharmacokinetics (García-Patterson et al, 2010; Goudie et al, 2014). Furthermore, increased efforts to achieve target glycaemia often increase the risk of severe hypoglycaemia, with potentially serious consequences for mothers (Evers et al, 2002). A nationwide study found that only 16% of women with type 1 diabetes achieved target glycaemia in early pregnancy, as defined by National Institute for Health and Care Excellence (glycated haemoglobin, HbA_{1c} <48 mmol/mol); this increases to 42% by late pregnancy (Murphy et al, 2021).

In addition to these physiological and pharmacological challenges, there is increased diabetes distress because of the enormous daily self-care burden. Pregnancy can be an anxious time for many women, and the added psychological challenges of managing type 1 diabetes in pregnancy should not be underestimated (Dahlberg and Berg, 2020).

How to cite this article:
Lee TTM, Murphy HR. What's new in the management of type 1 diabetes in pregnancy? Br J Hosp Med. 2022. https://doi.org/10.12968/hmed.2022.0412

Glucose monitoring in pregnancy and measures of maternal glycaemia

National Institute for Health and Care Excellence (2020) guidelines recommend HbA_{1c} measurement in early pregnancy to 'determine the level of risk to that pregnancy' in women with pregestational type 1 and type 2 diabetes, where an HbA_{1c} >48 mmol/mol confers increased risk. However, they do not recommend that HbA_{1c} be used 'to assess a woman's blood glucose control' during the second and third trimester. Outside of pregnancy, HbA_{1c} reflects average glycaemia over the preceding 8–12 weeks; however, in pregnancy, HbA_{1c} initially falls, owing to a drop in fasting glucose levels and higher erythrocyte turnover, before rising in late pregnancy, even as women spend more time in the target pregnancy glucose range (Feig et al, 2017). Despite these limitations, an above target HbA_{1c} after 24 weeks is associated with higher rates of preterm births, large for gestational age babies and neonatal care unit admissions, so should always be of concern (Murphy et al, 2021).

In addition to HbA_{1c}, pregnant women with type 1 diabetes traditionally monitor their glucose levels by sampling finger-stick capillary blood glucose at least seven times daily: fasting, before and 1 hour after each meal, and before bed, aiming for fasting glucose target of <5.3 mmol/litre and a 1-hour postprandial target of <7.8 mmol/litre if 'achievable without problematic hypoglycaemia' (National Institute for Health and Care Excellence, 2020). A 7- or 14-day average glucose can be obtained from capillary glucose meters, to provide some gauge of overall glycaemia. However, capillary glucose testing only gives snapshots of daily glycaemia, with limited reflection of glucose excursions between tests.

Continuous glucose monitoring

Over the last 20 years, newer technologies, known as continuous glucose monitoring systems, have become available. Continuous glucose monitoring systems consist of a subcutaneous sensor, which measures interstitial glucose, and a transmitter, which stores and sends the glucose data to a display device (which can be a specific receiver, smart phone or smart watch). With real-time continuous glucose monitoring, glucose levels can be measured at 5-minute intervals (almost 300 measurements a day) and are sent automatically to the display device. In contrast, intermittently scanned continuous glucose monitoring (commonly known as Flash) requires the user to scan a reader over the sensor to view stored glucose levels. Alarms and alerts can be set up to notify the user of any deviations in glucose level outside a set range (high or low). With real-time continuous glucose monitoring, levels can also be shared with their support networks (eg partners, parents).

Outside of pregnancy, continuous glucose monitoring has been shown to improve glycaemia, as measured by HbA_{1c}, without increased hypoglycaemia over capillary glucose monitoring and irrespective of mode of therapy (injections vs insulin pumps) (Battelino et al, 2012; Beck et al, 2017).

Newer continuous glucose monitoring systems are smaller and more user-friendly, and can replace traditional capillary glucose testing. Several systems are sufficiently accurate to be approved for insulin dosing and use while driving. Continuous glucose monitoring also provides users far greater insight into daily glycaemic excursions. Metrics calculated by continuous glucose monitoring-reporting software and ambulatory glucose profiles (a pictorial view of daily or average glycaemic patterns) (Figure 1) provide information to both users with diabetes and healthcare professionals, which they can then use to guide insulin dosing and lifestyle choices. In a study of 40 continuous glucose monitoring users, 87% changed their food choices using continuous glucose monitoring data, 48% modified their exercise routines and 90% stated that using continuous glucose monitoring contributed to a healthier lifestyle (Ehrhardt and Al Zaghal, 2020).

Continuous glucose monitoring in pregnancy

The continuous glucose monitoring in pregnant women with type 1 diabetes trial (CONCEPTT) was an international multi-centre randomised controlled trial, comparing capillary glucose monitoring with real-time continuous glucose monitoring. This is the largest trial evaluating the use of continuous glucose monitoring before and during

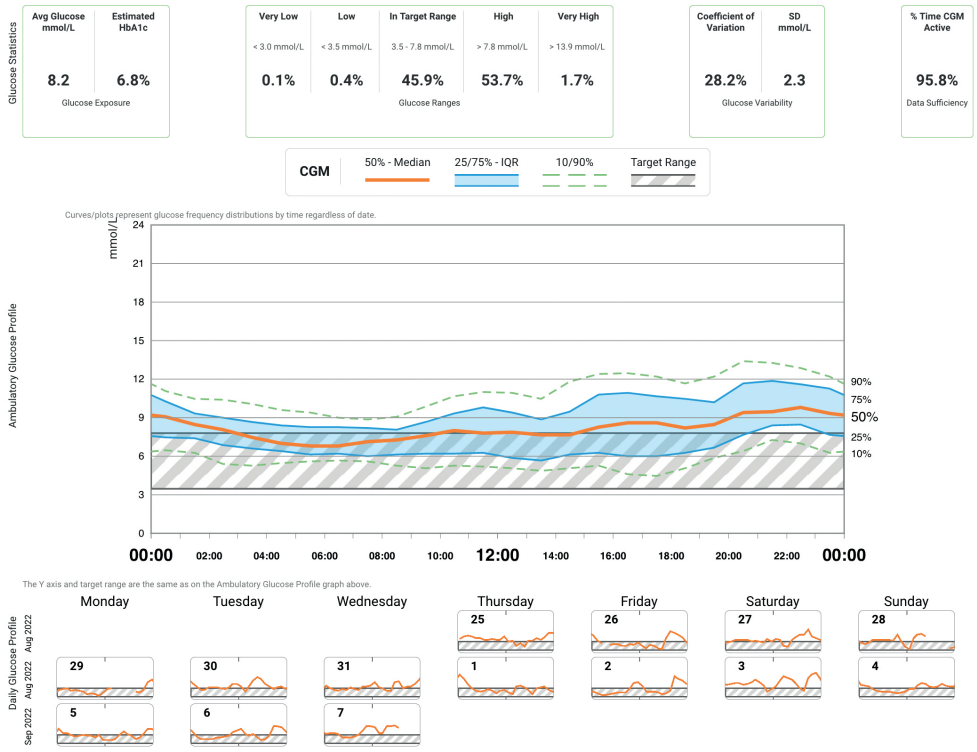

Figure 1. Example of a continuous glucose monitoring ambulatory glucose profile display during pregnancy.

pregnancy, and the first in which continuous glucose monitoring was used continuously from randomisation until delivery (in the pregnancy arm). Women using continuous glucose monitoring during pregnancy had improved glycaemia at 34 weeks' gestation, spending an increased percentage of time in the target glucose range of 3.5–7.8 mmol/litre and less time spent above target (>7.8 mmol/litre), with no increase in the duration or frequency of hypoglycaemia or severe hypoglycaemia or diabetic ketoacidosis events. Women using continuous glucose monitoring delivered fewer large for gestational age babies, with fewer neonatal care unit admissions of >24 hours and fewer neonatal hypoglycaemia events requiring treatment with intravenous dextrose (Feig et al, 2017). The number needed to treat was six to prevent one neonatal care unit admission or one large for gestational age baby and eight for neonatal hypoglycaemia, providing evidence for National Institute for Health and Care Excellence (2020) to recommend real-time continuous glucose monitoring for use in type 1 diabetes pregnancy.

Several continuous glucose monitoring metrics are useful in clinical care, including time in range, time above range, time below range, measures of glucose variability (coefficient of variation and standard deviation) and measures of overall glycaemia (average continuous glucose monitoring glucose and glucose management indicator). The Advanced Technologies and Treatments for Diabetes consensus created recommendations for target glucose levels. Based on data from CONCEPTT, these are time in range 3.5–7.8 mmol/litre >70%, with time above range <25% and time below range <5% from as early as possible in pregnancy (Figure 2) (Battelino et al, 2019).

A secondary analysis from CONCEPTT examined continuous glucose monitoring metrics from each trimester between women who used continuous glucose monitoring and those who used capillary glucose monitoring (with masked continuous glucose monitoring) (Tundidor et al, 2021). Although the majority of women did not meet the recommended continuous glucose monitoring targets, 10% of women achieved time in range >70% in the first and second trimesters and 35% by the third trimester (Tundidor et al, 2021). These data, together with data from Kristensen et al (2019), demonstrate that every 5% improvement still confers benefit (Murphy, 2019).

Access to continuous glucose monitoring data by patients and healthcare teams has added another dimension to management of type 1 diabetes in pregnancy. The value of

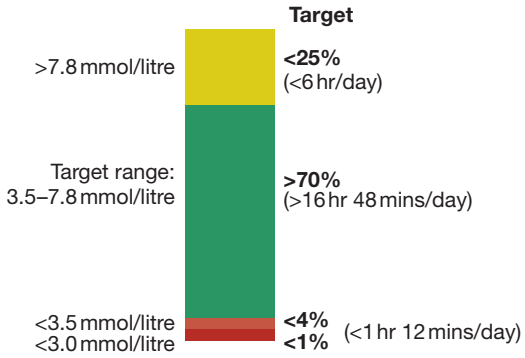

Figure 2. Continuous glucose monitoring targets for type 1 diabetes in pregnancy (adapted from Battelino et al, 2019).

continuous glucose monitoring in food selection and informing the timing of pre-meal insulin boluses is particularly important in achieving the pregnancy glucose targets. Furthermore, the real-time nature of continuous glucose monitoring and its capacity for customisable safety alerts to warn of impending hypoglycaemia, helps women to balance the risks of hypoglycaemia, which is harmful to the mother and is associated with obstetric and neonatal complications.

Insulin therapy in pregnancy

Women with type 1 diabetes administer insulin to manage their glucose levels in different ways. Most pregnant women use multiple daily injections, usually as basal-bolus regimens involving short and long-acting insulins, although more women are beginning to use insulin pumps, with approximately 33% using pumps before and during pregnancy (Murphy et al, 2021). Insulin pumps continuously infuse short-acting insulin subcutaneously. Infusion rates are set per hour to form a basal rate in lieu of long-acting insulin, and users administer prandial boluses via the pump.

Outside of pregnancy, insulin pump users have been demonstrated to have better glycaemia, fewer severe hypoglycaemic events and improved quality of life (Pickup, 2012). In pregnancy, the literature is inconsistent as to whether there is a benefit associated with the use of insulin pumps over multiple daily injections. A systematic review and Cochrane review of older studies concluded that there was no difference in maternal glycaemia (measured by HbA_{1c}) between pumps and injections and insufficient data for obstetric and neonatal outcomes (Ranasinghe et al, 2015; Farrar et al, 2016). More recently, an analysis of CONCEPTT participants found that women using multiple daily injections made greater glycaemic improvements, despite starting pregnancy with similar baseline HbA_{1c} (Feig et al, 2018). Continuous glucose monitoring data demonstrated that women using multiple daily injections also spent 5% more time in range during the mid-trimester (24 weeks) than insulin pump users, who did not catch up until 34 weeks. Insulin pump users developed more hypertensive disease (mostly gestational hypertension) and their infants had more neonatal hypoglycaemia and neonatal care unit admissions. They also reported less hypoglycaemia fear, although rates of hypoglycaemia were the same in both groups.

Closed-loop systems

More recently, there has been an increase in the use of closed-loop systems. Current iterations comprise three components:

1. Real-time continuous glucose monitoring
2. An algorithm that calculates and adjusts the basal insulin doses based on continuous glucose monitoring glucose levels every 10–12 minutes
3. An insulin pump that delivers insulin doses as calculated by the algorithm.

These can be referred to as a hybrid closed-loop system, as users still have to administer bolus insulin for meals and snacks, although some systems can also give automatically calculated boluses to correct hyperglycaemia in addition to user-directed boluses. The

glucose-responsive and glucose-predictive elements of algorithms act as built-in safety mechanisms, giving closed-loop therapy the potential to improve on standalone insulin pumps by facilitating achievement of time in range while minimising the risk of hypoglycaemia.

Outside of pregnancy, a meta-analysis of 40 studies assessing a variety of closed-loop systems in a wide range of settings found that time in range (3.9–10.0 mmol/litre) was higher with closed-loop therapy, both overnight and over 24 hours. These studies also were consistent with respect to hypoglycaemia, with significant reductions (20 minutes per 24 hours) of time spent below 3.9 mmol/litre (Bekiari et al, 2018).

In contrast, glycaemia in pregnancy is more complex, owing to changes with advancing gestation. In addition to increased insulin resistance during the second and third trimesters, there is more exaggerated daily variation (García-Patterson et al, 2010; Goudie et al, 2014). This, combined with the fact that so few women achieve the recommended pregnancy glucose targets using existing continuous glucose monitoring and insulin pump technologies, highlights the need for insulin therapies that can appropriately adjust for gestational changes.

Only one of the four commercially available closed-loop systems used in the UK is currently licenced for use in pregnancy (CamAPS FX). This system was developed and refined over four pilot closed-loop in pregnancy (CLIP) studies. The two earlier pilots focused on ensuring closed-loop components were accurate and able to function safely at early and late gestations and in response to exaggerated challenges of normal daily living (exercise, carbohydrate-rich meals and snacks) (Murphy et al, 2011a, b).

CLIP_03 was the first study to assess overnight closed-loop therapy use in the home setting (Stewart et al, 2016). Closed-loop therapy was compared with sensor-augmented pump therapy (in which continuous glucose monitoring is used alongside an insulin pump, but the insulin delivery is not automated in response to the continuous glucose monitoring). Closed-loop users spent >15% time in target range, with a lower mean glucose and minimal hypoglycaemia. This increase in time in range by 72 minutes per night in an unsupervised home setting demonstrated the potential of closed-loop therapy to help achieve and maintain the Advanced Technologies and Treatments for Diabetes consensus' recommended target of >70% time in range throughout pregnancy. CLIP_04 evaluated both day and night use of closed-loop therapy vs sensor-augmented pump therapy over 4 weeks in a broader patient population, including women with a higher HbA_{1c} in early pregnancy (Stewart et al, 2018). Despite higher baseline HbA_{1c} and added daytime challenges of meals, snacks, activity and user-directed prandial boluses, CLIP_04 women experienced less hypoglycaemia when using closed-loop therapy.

During both studies (used with earlier generation continuous glucose monitoring, insulin pumps and closed-loop algorithms), most women chose to continue using closed-loop therapy for the rest of their pregnancies. Many (27/32) continued using closed-loop therapy through labour and delivery and into the immediate postpartum period, which is a reflection of the system's acceptability to women. Overall, time in range was maintained at 70% throughout pregnancy, independent of baseline HbA_{1c} and previous insulin therapies (pumps or injections). Closed-loop therapy also performed well during vaginal births and elective and emergency caesarean sections, with women achieving a time in range of >80% during labour and delivery (3.5–7.8 mmol/litre) and the first 48 hours postpartum (3.9–10.0 mmol/litre) (Stewart et al, 2016, 2018).

Women reported feeling more empowered and in control of their daily glucose self-management, but this was balanced with increased vigilance and anxiety about the accuracy of the technology and potential glitches. Despite these concerns, the majority of participants worried less about overnight hypoglycaemia and felt that the system lessened the impact of their daily diabetes burdens.

Maternal glycaemia and insulin delivery during hospital admissions

During pregnancy, women with type 1 diabetes may require inpatient admission for diabetes and/or obstetric-related issues, including hypoglycaemia, diabetic ketoacidosis, hyperemesis gravidarum, suspected falling insulin requirements, fetal compromise or placental insufficiency. They may receive glucocorticoids for fetal lung maturation in

cases of suspected preterm delivery. Other indications include surgical procedures or other medical conditions (eg exacerbation of comorbid chronic disease or infection). The National Institute for Health and Care Excellence (2020) guidelines for diabetes in pregnancy recommend delivery of women with type 1 diabetes 'with no other complications' between 37 and 38+6 weeks' gestation by induction of labour or caesarean section, both of which require hospital admission. If the woman does labour spontaneously before the planned delivery date, National Institute for Health and Care Excellence (2017) guidelines for intrapartum care lists diabetes as a medical condition 'in which there is increased risk for the woman or their baby during or shortly after labour, where care in an obstetric unit would be expected to reduce this.'

These admissions all come with physiological or pathological stresses that affect maternal glucose levels and insulin sensitivity. Additionally, changes to daily routine, including hospital meals and reduced physical activity, also make insulin dose adjustments more challenging. The National Pregnancy in Diabetes Audit reported high and rising rates of severe hypoglycaemia events and diabetic ketoacidosis. At least one antenatal hospital admission for hypoglycaemia occurred in 14% of pregnancies, with diabetic ketoacidosis in 3% (NHS Digital, 2021). A national population-based case-control study examining diabetic ketoacidosis in pregnancy found that most events occurred during the third trimester, with the main precipitants being infection, vomiting, steroid administration and medication errors (Diguisto et al, 2022). Notably, half of the women remained euglycaemic during a diabetic ketoacidosis episode, and 15% of them experienced more than one episode during their pregnancy. There were high rates of perinatal mortality (16%) and greater risk of preterm delivery and neonatal care unit admissions.

In 2022, the Joint British Diabetes Societies for Inpatient Care (JBDS-IP) updated their guidance for the management of diabetes and hyperglycaemia during labour and birth (Dashora et al, 2022). While focusing on admissions for maternal steroid administration and delivery and birth, this guideline is widely used for the management of maternal glycaemia during other antenatal admissions.

Maternal corticosteroids are recommended for use in anticipation of preterm delivery for fetal lung maturation, as well as for reducing perinatal morbidity and mortality at the more extreme preterm gestations (Roberts et al, 2017). National Institute for Health and Care Excellence guidelines for preterm labour and birth recommend their use for deliveries up to 33+6 weeks' gestation, and consideration of their use up to 35+6 weeks (National Institute for Health and Care Excellence, 2019). Although diabetes should 'not be considered a contraindication to steroids for lung maturation' (National Institute for Health and Care Excellence, 2020), their use increases maternal hyperglycaemia (via insulin resistance and stimulation of liver gluconeogenesis) and risk of diabetic ketoacidosis for up to 5 days after their administration (Mathiesen et al, 2002). Long-term follow-up studies support the use of corticosteroid use before 34 weeks, as the benefits clearly outweigh the risks. However, this is not the case after 34 weeks, where 35 mothers need to be treated to prevent one mother needing respiratory support 3 days after delivery (Gyamfi-Bannerman et al, 2016). Given the increased risk of preterm delivery in women with type 1 diabetes, it is important to be aware of the benefits and risks of corticosteroids and how the balance of these change at different gestations.

Maintaining target glycaemia during labour and delivery was initially thought to be important in reducing the risk of neonatal hypoglycaemia (Ryan and Al-Agha, 2014). However, more recent work found no association between intrapartum maternal hyperglycaemia and neonatal hypoglycaemia (Yamamoto et al, 2018, 2020). Particular challenges to managing maternal glycaemia during labour and delivery, be it vaginal or by caesarean section, include changes in cortisol and, if labouring, the use of glucose by uterine contractions. As in other settings, the pursuit of target glucose levels comes with increased risks of maternal hypoglycaemia. In response to this, the JBDS-IP offers guidance that supports both the traditional intrapartum targets (as recommended by National Institute for Health and Care Excellence, which is 4.0–7.0 mmol/litre) and an updated range of more relaxed targets (5.0–8.0 mmol/litre). The alternative targets of 5.0–8.0 mmol/litre may help to reduce the risk of maternal inpatient hypoglycaemia (as recommended in other inpatient settings), and reduce the use of variable rate intravenous insulin infusion, which adds

burden to obstetric and midwifery staff who are not specifically trained in inpatient diabetes management. A reduction in variable rate intravenous insulin infusion use also reduces potential complications including electrolyte imbalance, fluid overload and unrecognised maternal hypoglycaemia on a busy delivery unit, which can have disastrous consequences (Table 1) (Dashora et al, 2022).

For women with diabetes, the use of variable rate intravenous insulin infusion is also often felt to be invasive and disempowering, where control over their diabetes self-management is 'taken away' and left 'in the hands' of inexperienced obstetric ward staff.

There is a rapid increase in insulin sensitivity as soon as the placenta is delivered, with some women experiencing transient insulin independence, especially in the first 24–48 hours postpartum (Achong et al, 2014). To minimise the risk of severe hypoglycaemia and meet the non-pregnancy glucose targets (3.9–10.0 mmol/litre, but often relaxed to 6.0–10.0 mmol/litre during the postnatal inpatient stay), a postnatal insulin plan should be agreed with the patient and documented in advance. Because of the variability in the reduction of insulin doses, there are several options for postnatal insulin regimens, based on reductions in pre-pregnancy or early pregnancy doses or half of late pregnancy doses. If variable rate intravenous insulin infusion is used, the rate of insulin infusion should be halved immediately after delivery of the placenta. This is supported by closed-loop data, which demonstrated substantial person-to-person variability and postnatal total daily insulin requirements of approximately half that of late pregnancy.

Last, with the increase in the use of diabetes technology, the JBDS-IP update includes practical advice and safety recommendations regarding continuous glucose monitoring and insulin pump use for inpatients, including those in the operating theatre for delivery by caesarean section. This advice empowers women and their accompanying support person to safely self-manage their diabetes if they are able and wish to do so.

Conclusions

Managing diabetes in pregnancy is challenging and, although our understanding continues to improve, obstetric and neonatal complications still occur at high rates. Pregnancy can be an exciting and happy time, but women with type 1 diabetes are often overwhelmed by the increased challenges to diabetes self-management, concerns about potential complications and feelings of frustration, burnout and failure when their glucose levels are out of target.

Table 1. Potential complications associated with the use of variable rate intravenous insulin infusion on maternity wards

Stage of use of variable rate intravenous insulin infusion	Potential complications
Variable rate intravenous insulin infusion initiation	■ Delayed commencement leading to insufficient time to minimise neonatal hypoglycaemia and/or diabetic ketoacidosis ■ Use of wrong connectors ■ Lack of use of one-way anti-siphon valves ■ Incorrect programming
Variable rate intravenous insulin infusion implementation	■ Resource intensive and limits autonomy for diabetes self-management during birth ■ Insufficient blood glucose measurements resulting in either hypoglycaemia or hyperglycaemia ■ Titration scales that predispose to hypoglycaemia ■ Premature cessation of the substrate but with the continuation of intravenous insulin infusion leading to hypoglycaemia ■ Hyponatraemia as a result of inadequate sodium in substrate fluid ■ Fluid overload ■ Erroneous blood glucose measurements caused by use of glucose in arterial flush lines
Variable rate intravenous insulin infusion cessation	■ Careful timing of pre-meal and basal subcutaneous insulin needed

Adapted from Dashora et al (2022)

Key points

- Diabetes management is uniquely challenging in pregnancy, as pregnant women must strive to achieve the pregnancy glucose targets of 70% time in range to minimise the risk of obstetric and neonatal complications.
- Diabetes technologies are being increasingly used during pregnancy and can empower women to self-manage their diabetes, both at home and during inpatient hospital settings, including acute antenatal admissions and during labour and birth.
- It is important for healthcare professionals in the acute hospital setting to understand these new technologies and work with women to determine when to step in and take over their management and when to step back and support their self-management during hospital admissions.

With the rapid advances in diabetes technologies, their increased use in clinical care and inclusion in national guidance, there is a need for inpatient hospital teams to integrate support for users of these technologies into care pathways and the training of healthcare professionals. The advent and development of maternal medicine networks will assist all members of the multidisciplinary team, from maternity and general medicine, to work more closely together and improve the care and support provided to women with medical conditions during pregnancy.

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Conflicts of interest

HR Murphy sits on the Medtronic European Scientific Advisory Board and reports speaker honoraria from Dexcom, Abbott, Medtronic and Novo Nordisk; TTM Lee is funded by a Diabetes Research & Wellness Foundation Sutherland-Earl Clinical Fellowship (reference SECF/21) and declares no conflicts of interest.

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