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Review Article

# A Review of Diabetes Technology During Pregnancy in Women with Pregestational Diabetes Mellitus

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## Abstract

Diabetes technology is the use of devices such as continuous glucose monitoring (CGM) systems, continuous subcutaneous insulin infusion (CSII) pumps, and hybrid closed-loop systems with a goal to help manage blood glucose levels, prevent diabetes complications, and improve the quality of life of patients burdened by this disease. The use of diabetes technology is long-standing, as clinicians have continued to study these devices to establish a safe and accurate method of glucose control for patients with pregestational diabetes during pregnancy. Diabetes technology has advanced dramatically within the last decade, making it imperative to establish safety and accuracy during pregnancy in patients with pregestational diabetes. The purpose this literature review is to provide the field of Obstetrics and Gynecology with evidence-based maternal fetal medicine on the use of diabetes technology in these patients, especially if they have been on these devices with excellent glycemic control prior to pregnancy. This will hopefully be helpful to Obstetricians and Gynecologists to determine when diabetes technology is an appropriate option for management of their patients with pregestational diabetes to improve maternal and neonatal health outcomes.

***Keywords:*** *Diabetes Technology; Continuous Glucose Monitoring (CGM); Continuous Subcutaneous Insulin Infusion (CSII); Hybrid Closed-Loop; Pregnancy; Pregestational Diabetes; Type 1 Diabetes*

## Introduction

The Centers for Disease Control and Prevention (CDC) states, based on data published in 2019 by Azeez., *et al*. that the overall prevalence of diabetes, both type 1 and type 2, among non-pregnant women of reproductive age is 4.5% [1]. Of those women with diagnosed diabetes (3.2%), 51.5% had uncontrolled diabetes [1]. Type 1 diabetes is the immune-mediated destruction of pancreatic β-cells, the cells responsible for insulin production, causing an insulin-deficient state and hyperglycemia [2]. Type 2 diabetes is characterized by a defect in the insulin-producing pancreatic β-cells and an inability for tissues to respond to insulin secretion appropriately, leading to resistance [3]. According to the American College of Obstetricians and Gynecologists (ACOG), pregestational diabetes is observed in 1 - 2% of pregnancies [4]. Pregestational diabetes mellitus is defined as type 1 or type 2 diabetes mellitus that has been diagnosed prior to pregnancy. Diabetes diagnosed during pregnancy is also termed as pregestational if diagnostic criteria, table 1 are met in the first or early second trimester, prior to 24 weeks gestation [4].

| Diagnostic Criteria | Value |
|---|---|
| Hemoglobin A1C | ≥ 6.5% |
| Fasting Plasma Glucose Concentration | ≥ 126 mg/dL |
| Two-hour postprandial glucose* | ≥ 200 mg/dL |

***Table 1:*** *Criteria for pregestational diabetes diagnosed in the first or early second trimester.*

**After 75-g oral glucose tolerance test.*

Physiologic changes during pregnancy affect glucose metabolism, creating a diabetogenic state. During the early first trimester, glucose is shunted from the maternal circulation to the fetus to aid in its development, while the maternal metabolism works to adapt and maintain glucose levels [5]. Concurrently, insulin secretion and insulin sensitivity increase due to hyperplasia of pancreatic beta-cells [5]. These physiological changes increase a pregnant woman's risk of hypoglycemia (serum blood glucose < 70 mg/dL), which if asymptomatic or left untreated, may lead to maternal injury and even death. Pregnancy blunts the response of epinephrine and glucagon, the hormones responsible for generating symptoms of hypoglycemia such as tachycardia, weakness, diaphoresis, and pallor, masking their effects [5]. An increased catabolic state, pregnancy also generates a stress-like physiologic response and increases the risk of ketoacidosis due to lipolysis and subsequent ketogenesis, as large lipids are impermeable to the placenta, thus ketones are transferred to the fetus to be used for energy [5]. Beginning in the second trimester and peaking in the third trimester of pregnancy, the increase of progesterone, estrogen, cortisol, and placental hormones including human chorionic gonadotropin (hCG), human placental lactogen (hPL), and human placental growth hormone (hPGH) create a state of insulin resistance, putting patients at risk of severe hyperglycemia (serum blood glucose >/= 140 mg/dL) [6]. hPGH may mimic the role of growth hormone (GH), creating an impaired response to insulin like that of type 2 diabetes, leading to decreased glucose uptake, hyperinsulinemia, and increased glycogen synthesis [7]. With advancing gestation, a 50 - 60% decrease in insulin sensitivity is seen [7]. The intrapartum state of pregnancy is also a time of high insulin resistance, as insulin antagonistic hormones such as corticotropin releasing hormone (CRH) and cortisol are released to promote uterine muscle contractility [5]. During labor, relaxin is released which promotes insulin sensitivity [5]. After delivery, there is a sudden increase in insulin sensitivity and decrease in insulin resistance due to the quick decrease in placental hormones, and insulin requirements decrease drastically [5]. The recommendations for insulin after delivery is one-third to one-half of predelivery dose for both long-acting and short-acting insulin [4].

Pregestational diabetes mellitus is known to cause complications during pregnancy that lead to adverse health outcomes in both a mother and fetus. For this reason, pregnant women with this disease must be frequently monitored and insulin treatment must be adjusted to decrease the possibility of such outcomes. Congenital malformations occur in 6 to 12% of women with pregestational diabetes, as uncontrolled hyperglycemia affects early organ development including that of the heart, brain, spine and skeleton [8]. Women who have pregestational diabetes mellitus may develop chronic hypertension or microvascular disease during pregnancy that can lead to preeclampsia and eclampsia. In pregnant women with type 1 diabetes without nephropathy, preeclampsia is observed 15 - 20% of cases, and up to 50% in those with nephropathy [4]. Within inadequate glycemic control, diabetic nephropathy and retinopathy progress in pregnancy, which can lead to end-stage renal disease and blindness. Increased serum blood glucose levels increase the amount of amniotic fluid in the amniotic sac that surrounds the fetus, which can lead to preterm labor [8]. Higher HbA1c values are strongly correlated with fetal macrosomia and increase the risk of cesarean birth [4]. Neonates born to mothers with pregestational diabetes mellitus are at increased risk of developing hypoglycemia, respiratory distress syndrome, and hyperbilirubinemia, all of which increase admissions to the neonatal intensive care unit (NICU) [4].

Glycemic control prior to conception has been proven to be the most significant factor that influences hyperglycemia during pregnancy in patients with pregestational diabetes and the complications that can develop. The first eight weeks of pregnancy, a time when many

women do not know they are pregnant, are the most crucial for organ development. Controlling glucose prior to conception is important to prevent birth defects. Severe hyperglycemia, along with a high basal-bolus insulin regimen prior to pregnancy, directly correlates with worse glycemic control during pregnancy and increased incidence of fetal malformations and perinatal mortality [9]. A HbA1c concentration of nearly 10% is associated with a fetal anomaly rate of 20 - 25% [4]. Previous studies have provided evidence that a reduction of HbA1c to a normal range (ideally 6.0%) between preconception counseling and confirmation of pregnancy leads to better glycemic control during pregnancy and prevention of congenital abnormalities [10]. Through preconception counseling, clinicians evaluate baseline conditions to determine if glycemic control is adequate to proceed with attempts to conceive. Prior to conception, routine blood pressure checks, retinal examination, 24-hour urine collection for protein excretion and creative clearance, lipid assessment, and electrocardiography are performed to determine the risk of diabetic pregnancy complications [4]. Plans are created between the patient and clinician to reach healthy BMI through diet and exercise to optimize HgbA1c. Patients are also prescribed 400mcg of folic acid to help prevent neural tube defects [4]. However, despite efforts to optimize glycemic control in women of reproductive age prior to conception, this counseling evaluation often does not occur prior to unintended pregnancies.

As published by the Guttmacher Institute, 45% of 6.1 million pregnancies that occur in the U.S. each year are unintended, highlighting the importance of obtaining tighter glucose control in women of reproductive age diagnosed with type 1 or type 2 diabetes [11]. Although pre-pregnancy care is an integral part of controlling diabetes during pregnancy, it does not reduce complications seen in later stages of pregnancy as the physiologic changes that occur during pregnancy alter control of blood glucose and insulin sensitivity. As pregnancy progresses, so do insulin requirements. In the first trimester, the body needs 0.7 - 0.8 units/kg actual body weight per day, 0.8 - 1 units/kg/day in the second trimester, and 0.9 - 1.2 units/kg/day in the third trimester [4]. In women that conceive with serum blood glucose levels that are uncontrolled, it becomes a challenge to improve glycemic levels and deliver the insulin requirements demanded by pregnancy. Often, the traditional approaches of self-monitoring blood glucose (SMBG) and multiple daily doses of insulin (MDI) fail to take control of hyperglycemia and deliver the amounts of basal and bolus insulin needed by the body.

In settings where traditional approaches fail to improve glycemic control before or during pregnancy, providers can turn to diabetes technology in the form of continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM), and hybrid closed-loop systems, which may offer a better solution for glycemic control during preconception, pregnancy, and labor. While diabetes technology has not yet been approved by the U.S. Food and Drug Administration (FDA) for use in pregnancy, they are currently being used by clinicians off-label, and there is published evidence suggesting that its utilization can optimize blood glucose levels during pregnancy safely and achieve glycemic control that is otherwise not possible through SMBG and MDI. This paper is a review article of published data to provide us with more information on the use of diabetes technology during pregnancy in women with pregestational diabetes, the advantages and disadvantages of their use, and their effect on maternal and neonatal health outcomes.

## Methods

The PubMed Database was used to research literature published with a focus on the use of technology in pregestational diabetes mellitus during pregnancy. The following search terms were used alone and in combination: type 1 diabetes, type 2 diabetes, pregestational diabetes, multiple daily doses of insulin, continuous glucose monitoring, continuous subcutaneous insulin infusion, insulin pump, hybrid closed-loop, preconception, during pregnancy, during labor, maternal outcomes, fetal outcomes, and neonatal outcomes. Data on diabetes technology was used from information published on diabetic medical device company websites and telephone calls with company representatives including Medtronic, Insulet Corporation (Omnipod), Dexcom, Abbott (Freestyle Libre), Ascensia Diabetes Care and Tandem Diabetes Care.

## Review of diabetes technology

### Continuous subcutaneous insulin infusion

Both ACOG and ADA recommend Insulin as the traditional first-line drug used to control blood sugar during pregnancy, as it is the most effective for fine-tuning of blood sugar and is a safe choice for the fetus, as it does not cross the placenta. Insulin can be injected with a syringe, an insulin pen, or through an insulin pump, all of which are safe to use in pregnancy. Continuous subcutaneous insulin infusion (CSII) therapy is the delivery of insulin through an external insulin pump which provides a steady stream of insulin into the body. It contains an insulin-filled reservoir cartridge, which is connected to a cannula that is inserted into subcutaneous tissue and is programmed to provide basal insulin infusion, prandial insulin boluses, and correction insulin boluses [12]. Currently, there are three CSII manufacturers in the diabetes technology market in the United States: Medtronic, Tandem Diabetes Care, and Insulet Corporation.

An insulin pump has advantages in that it allows the wearer to take instantaneous action to help increase or decrease blood glucose levels. CSII has increasingly been studied to discover the possible benefits in treating pregestational diabetes in pregnancy, comparing it to its counterpart MDI. The UK National Institute for Health and Care Excellence (NICE) recommends that women with insulin-treated diabetes should be offered insulin pump therapy during pregnancy if they are unable to achieve adequate blood glucose control using MDI [13]. The use of CSII allows for more precise and greater insulin dosing flexibility, which is not possible with MDI. CSII can mimic the physiology of the body as it has a programmed basal and bolus insulin delivery system that can titrate dosages based on meals and activity, which is otherwise not as greatly achieved through MDI. Despite its convenience and achievability, if not managed properly CSII can pose some disadvantages. The infusion site set must be changed every 2 - 3 days and its location must be rotated to prevent site infection [14]. Malfunction of the device can occur which can alter insulin delivery and subsequently lead to life-threatening hypoglycemia, hyperglycemia, or diabetic ketoacidosis [14]. Given that pregnant patients are a high-risk population, there have not been randomized control trials with large sample sizes that can distinguish whether MDI or CSII is better. However, several clinical studies with smaller populations have shown that CSII can be advantageous in pregnancy.

### CSII during pregnancy

In a retrospective multicenter study conducted by Bruttomesso., *et al.* on 144 pregnant women with type 1 diabetes, patients that were on CSII achieved a lower HgA1c at the end of their 1$^{st}$ trimester compared to their MDI counterparts ($p = 0.02$) and required significantly required less insulin treatment ($p < 0.01$) [15]. Although the HgA1c did lower similarly for both groups by the end of the 3$^{rd}$ trimester, the CSII group was able to do so with lower total daily insulin requirements [15]. In a retrospective cohort study published by Smrz., *et al*. including pregnant women with type 1 diabetes, it was determined that CSII significantly decreased both early A1c (< 20 weeks) and late HbA1c (> 20 weeks) during pregnancy ($p = 0.008$), however, it had greater variability in glucose measurements when compared to MDI [16]. One of the advantages of CSII in non-pregnant patients with diabetes is that it decreases glycemic variability [14], however based on one of the outcomes of this study, this may differ for pregnant patients.

Prior., *et al*. published a retrospective cohort study of 110 pregnant women with type 1 diabetes, finding that those who were on MDI required significantly higher doses of basal insulin at all time points when compared to those on CSII ($p < 0.001$), while bolus insulin was similar between both groups [17]. This outcome is like that found in another retrospective study on 53 women published by Mello., *et al.* finding that women on MDI needed higher daily doses of insulin than the CSII group ($p = 0.007$) [18]. Prior., *et al.* also concluded that higher insulin dosage regimens were associated with a higher incidence of hypoglycemia, as women on CSII spent less time-in-range in hypoglycemia (< 70 mg/dL) [17]. Jotic., *et al*. had a similar outcome in their observational cohort study performed on 128 pregnant women with type 1 diabetes, showing that women on CSII had significantly less hypoglycemia than women on MDI [19]. This suggests that CSII may be advantageous in decreasing frequency of hypoglycemia during pregnancy.

### CSII during labor

Time of delivery of women with pregestational diabetes differs based on glucose control and associated comorbidities. In women with well-controlled diabetes, delivery is recommended around 39 0/7 weeks, while women with poor glucose control and associated comorbidities, such as vasculopathy or nephropathy, are recommended to deliver between 36 0/7 weeks and 38 6/7 weeks [4]. Upon induction of labor, women with pregestational diabetes are put on an IV infusion of short-acting insulin with normal saline to titrate blood glucose to less than 110 mg/dL [4]. Short-acting insulin with normal saline is administered at a rate of 1.25 units/h if glucose levels exceed 100 mg/dL. If glucose drops below 70 mg/dL, normal saline is changed to 5% dextrose and is infused at a rate of 100 - 150 cc/h [4]. Women who are on a CSII pump may continue to be on their pump while in labor, however protocol varies between hospitals. In hospitals with established protocols that include the use of an insulin pump, there is a designated individual or team to control the pump. In hospitals without such a protocol that may have less resources and less staff to control the pump, such is not the case. Although not clinically indicated, women who are on CSII pumps during pregnancy are often taken off the pump and placed on IV insulin.

Studies have shown that patients on CSII have better mean glycemic control during labor and delivery when compared to IV insulin. A retrospective cohort study performed by Drever., *et al*. including 161 pregnancies of women with type 1 diabetes, investigated the safety and efficacy of CSII during labor and delivery [20]. They compared outcomes of three groups, women on pumps who stayed on pumps during labor, women on pumps who switched to IV insulin infusion during labor, and women on MDI who switched to IV insulin infusion during labor and delivery [20]. Women in the pump/pump group during pregnancy were of older age, had a longer duration of diabetes, and a lower HbA1c in both the first and third trimesters of pregnancy [20]. Those who had a lower 3$^{rd}$ trimester HbA1c were the women who chose to remain on the pump during labor and delivery [20]. These women also had significantly better mean glucose during labor ($p = 0.01$) than those who switched to IV insulin and had better median glucose and spent more time in target range, although not significant [20]. The outcomes of this study suggest that CSII can maintain blood glucose levels in target range during labor.

### CSII and maternal-neonatal outcomes

Mantaj., *et al.* performed a retrospective study on 297 infants born to women with type 1 diabetes to investigate if CSII is advantageous to MDI to improve maternal metabolic control during pregnancy and decrease adverse neonatal outcomes [21]. Maternal outcomes including gestational week at delivery, miscarriage, or intrauterine fetal death (> 22 weeks) were similar between both groups. Newborns born to CSII mothers showed a significant reduction in abnormal birth weight outcomes and adverse neonatal outcomes including malformations, emergency cesarian section, prematurity, RDS, hypoglycemia, and hyperbilirubinemia ($p = 0.01$) [21]. Although it was not statistically significant, an upward trend was found in the first minute APGAR score of newborns born to mothers on CSII [21]. Additionally, four out of five women who suffered from late pregnancy loss in this study were on MDI with inadequate glycemic control through the pregnancy [21]. In a retrospective study observational study on 34 pregnant women with type 1 diabetes, Talaviya., *et al*. found that newborns of mothers on CSII had a statistically significant increase in 1-min APGAR score when compared to newborns of MDI mothers ($p < 0.05$) [22]. The rate of preterm labor, caesarian section and hypoglycemia was also decreased in CSII mothers, however not statistically significant [22]. Mourou., *et al.* retrospectively assessed maternal and neonatal outcomes in pregnant women with type 1 diabetes who had a planned versus unplanned pregnancy, finding that CSII performs better with pre-pregnancy planning [23]. They found that women on CSII who had a planned pregnancy had a statistically significant lower outcome of preterm delivery when compared to women with an unplanned pregnancy ($p = 0.01$) [23]. As one would expect, premature newborns had higher NICU admissions than newborns that were full-term ($p = 0.002$) [23]. Women on CSII with a planned pregnancy also had a lower HbA1c during all three trimesters of pregnancy, suggesting that these women and their newborns had better outcomes because they had better glucose control during their pregnancy [23].

## Continuous glucose monitoring

Blood glucose monitoring is the primary tool used to determine if one's blood glucose levels are in target range. The ADA recognizes self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM), and hemoglobin A1C as methods of assessing glycemic control [24]. SMBG involves collecting a drop of blood via fingerstick onto a test strip and inserting the test strip into a glucose meter which displays a number on its screen representing capillary glucose. CGM is a device that continually monitors glucose levels for a predetermined number of days and measures glucose levels from as frequently as every minute up to every 5 minutes, recording up to 288 values a day [12]. This device works via a sensor that is placed under the skin, usually on the posterior upper arm or abdomen, which measures glucose of the interstitial fluid [12]. The data is recorded and sent via a transmitter to a device such as a reader, smartphone application, or insulin pump, allowing patients and providers to keep track of glucose [12]. CGMs have a feature that alerts patients at the time of, or in advance, of a hypoglycemic or severe hyperglycemic episode which can help them take corrective action to prevent these episodes from worsening [12]. There are two types of CGM including retrospective CGM (r-CGM), which examines the blood glucose profile over several days, and real-time CGM (RT-CGM), which confirms blood glucose profile in real-time, or in the moment [25]. Currently, there is one r-CGM system, Free Style Libre 14 Day, and four RT-CGMs, Dexcom G6, Medtronic Guardian, Free Style Libre 2, and Ascensia Eversence. All devices have not been approved by the FDA for their use in pregnant women. Although not FDA approved, the Dexcom G6 and FreeStyle Libre 2 have been CE marked for use in pregnancy in Europe [26]. NICE recommend offering RT-CGM to all pregnant women with type 1 diabetes to help meet their blood glucose targets [26].

Target goals for self-monitoring blood glucose levels during pregnancy have been established by the American College of Obstetricians and Gynecologists (ACOG) and American Diabetes Association (ADA) (Table 2) [4]. These targets differ from the targets of continuous glucose monitoring. The ADA has established guidelines for glycemic control during pregnancy in patients using CGM (Table 3) [27]. These guidelines are based on time in range, the percentage of time spent with serum blood glucose levels in the set target range, defined as 63 to 140 mg/dL by the ADA. For optimal obstetric and neonatal outcomes, it is recommended that women and clinicians aim for a TIR > 70% (16h, 48 min) and a TAR, time above range, of < 25% (6h), as displayed in figure 1, and these targets should be achieved as early as possible in pregnancy [27]. There is limited evidence on the appropriate TIR, time below range (TBR), and TAR for pregnant women with type 2 or gestational diabetes [27]. ACOG has yet to establish guidelines for TIR, TBR, and TAR in pregnancy for patients using CGM, however they recommend tighter glycemic control during pregnancy than the recommendations set by the ADA for patients using CGM.

| Glucose Type | Glucose Concentration |
|---|---|
| Fasting glucose | ≤ 95 mg/dL (5.3 mmol/L) |
| Pre-prandial glucose | ≤ 100 mg/dL (5.6 mmol/L) |
| One-hour postprandial glucose | ≤ 140 mg/dL (7.8 mmol/L) |
| Two-hour postprandial glucose | ≤ 120 mg/dL (6.7 mmol/L) |
| Mean capillary glucose | 100 mg/dL (5.6 mmol/L) |
| Overnight glucose | ≥ 60 mg/dL |

***Table 2:*** *ACOG and ADA recommendations for SMBG levels during pregnancy.*

| | TIR | | TBR | | TAR | |
|---|---|---|---|---|---|---|
| Diabetes Group | % of readings; time per day | Target range | % of readings; time per day | Below target level | % of readings; time per day | Above target level |
| Pregnancy, Type 1 | > 70%; > 16h, 48 min | 63 - 140 mg/dL (3.5 - 7.8 mmol/L) | < 4%; < 1h<br>< 1% < 15 min | < 63 mg/dL (< 3.5 mmol/L)<br>< 54 mg/dL (< 3.0 mmol/L) | < 25%; < 6h | > 140 mg/dL (> 7.8 mmol/L) |
| Pregnancy, Type 2 | See CGM text | 63 - 140 mg/dL (3.5 - 7.8 mmol/L) | See CGM text | < 63 mg/dL (< 3.5 mmol/L)<br>< 54 mg/dL (< 3.0 mmol/L) | See CGM text | > 140 mg/dL (> 7.8 mmol/L) |

***Table 3:*** *ADA guidelines for glycemic control during pregnancy in patients using CGM.*

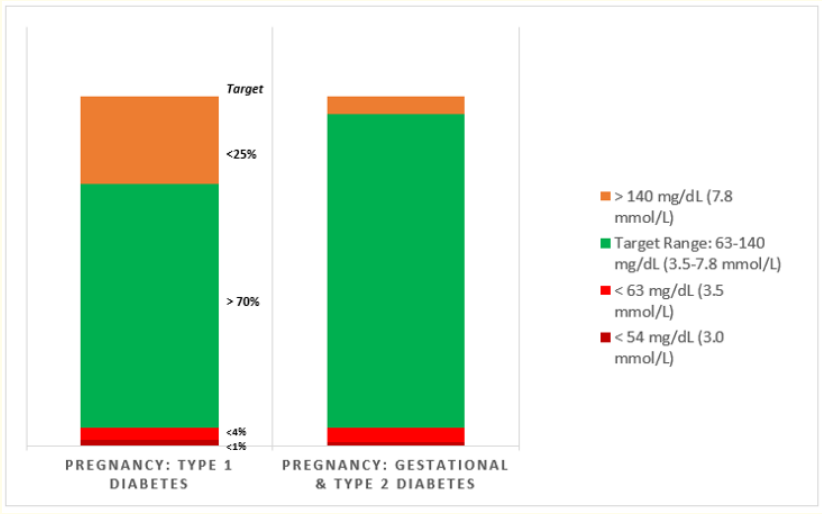


***Figure 1:*** *CGM-based glycemic targets for pregnant patients with diabetes.*

## CGM during pregnancy

The CONCEPTT trial conducted by Feig., *et al.* was a multicentre, open-label, randomized controlled trial that was performed on 325 women of reproductive age with type 1 diabetes who were pregnant or planning a pregnancy and receiving intensive insulin therapy [28]. Women were randomly assigned to either capillary glucose monitoring with RT-CGM or capillary glucose monitoring alone. Pregnant women on RT-CGM were found to have a decrease in HgbA1C during pregnancy, spent significant more time in target range ($p = 0.0207$) and less time in hyperglycemia ($p = 0.0279$), had less glycemic variability at 34 weeks gestation and comparable hypoglycemic episodes with women who were not on CGM [28]. The most common adverse effect that occurred in CGM participants were skin reactions (48%) [28].

In a one-center, observational study conducted by Lason., *et al.* on 81 pregnant women with type 1 diabetes, women on both CSII and CGM, compared to those on CSII without CGM and MDI, had the lowest HgbA1c levels during all three trimesters and their postpartum

visit (p = 0.003, p = 0.030, p = 0.039 and p = 0.002) [29]. Polsky., *et al.* conducted a small prospective study on 36 pregnant women with type 1 diabetes to assess whether pregnant women on Dexom G6 RT-CGM Share (remote monitoring by followers), CGM alone, or no CGM has better glycemic control [30]. While HbA1c decreased in all women during pregnancy, those using CGM Share had a significantly lower HbA1c overtime when compared to those on CGM alone or no CGM (p = 0.0042) [30]. Women on CGM Share also had lower median sensor glucose levels (p = 0.331) and spent less time above target range (p = 0.0228) [30]. This suggests that CGM can have better outcomes during pregnancy when there are family or friends that can help women remain accountable during their pregnancy through remote monitoring. Polsky., *et al.* also reported an overall 92.5% accuracy of CGM glucose measurements when compared to SMBG [30]. Figure 2 illustrates how glucose data is presented by SMBG versus CGM.

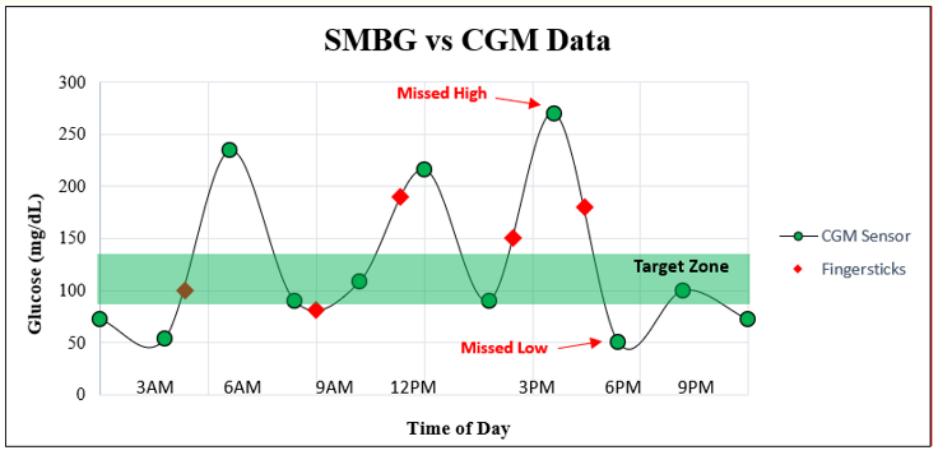


***Figure 2:*** *Self-monitoring blood glucose vs continuous glucose monitoring data.*

**This figure is for illustration purposes only. Microsoft Office was used to create this illustration.*

*Description: This graph illustrates the advantage of the CGM sensor over SMBG via fingerstick, as continuous monitoring of blood glucose records data every few minutes, detecting moments of hypoglycemia or hyperglycemia that can be missed by fingerstick measurements.*

## CGM during labor

ACOG recommends a capillary blood glucose target over 70 mg/dL and up to 100 mg/dL during labor to avoid risk of neonatal hypoglycemia [4]. The ADA recommends that women who are on CGM during pregnancy should continue to use CGM during labor, as the sensor can help detect hypoglycemia that may be missed with finger sticks [27]. Glycemic targets for CGM specifically for labor have not been established by the ADA or ACOG, however there is a need for tighter control during labor to prevent neonatal hyperinsulinemia and hypoglycemia.

## CGM and maternal-neonatal outcomes

In women with type 1 diabetes, an incremental increase of 5% in time in range (TIR) has been associated with clinically significant benefits in pregnancy [27]. The CONCEPTT trial, mentioned previously in this paper, showed a significant difference on neonatal health outcomes in pregnant women on CGM. In pregnant women with type 1 diabetes who were using RT-CGM, there was a decrease in the incidence of large for gestational age (p = 0.0210), NICU admissions longer than 24 hours (p = 0.0157), neonatal hypoglycemia (p =

0.0250), and length of hospital stay (p - 0.0091) [28]. The GlucoMOMS trial conducted by Voormolen., *et al*. was a nationwide multicentre, open label, randomized controlled trial on 300 pregnant with type 1, type 2, or gestational diabetes that were undergoing insulin therapy and placed on retrospective CGM or no CGM at all [31]. They found that the incidence of macrosomia did not decrease with the use of CGM [31]. Additionally, the incidence of preeclampsia was lower in women who were on CGM (p = 0.06), and HELLP syndrome did not occur in any patients on CGM, while it occurred in 4 women that were not on CGM (p = 0.10) [31]. Lason., *et al.* found that despite very good glycemic control, pregnant women on CSII and CGM had a high risk of macrosomia (19.7%) [29]. In a meta-analysis conducted by Garcia-Moreno., *et al.* on 6 randomized clinical trials which included 482 pregnant patients, women using CGM had less gestational weight gain and children had lower birth weight, but no differences were observed in macrosomia [32].

## Hybrid closed-loop systems

CSII can be used concurrently with a CGM, referred to as sensor-augmented pump therapy. Since the inception of the first sensor-augmented insulin pump, technology has continued to advance, and we now have availability of what is known as hybrid closed-loop (HCL) insulin delivery (Figure 3a). In a HCL system, the CGM delivers glucose data to a modulator which has an algorithm that determines how much insulin should be delivered via the pump (Figure 3b) [12]. The desired outcome of an HCL system is to automatically adjust basal insulin delivery to prevent hypoglycemia and hyperglycemia, however the patient is still responsible for bolus insulin delivery. Hybrid closed-loop systems currently available are the Medtronic MiniMed 770G system, Omnipod 5, and the Tandem t:slim X2 insulin pump with Control-IQ technology. HCL is the only type of automated insulin delivery system that has been studied off-label in pregnancy, however no model has approved for management of diabetes during pregnancy.

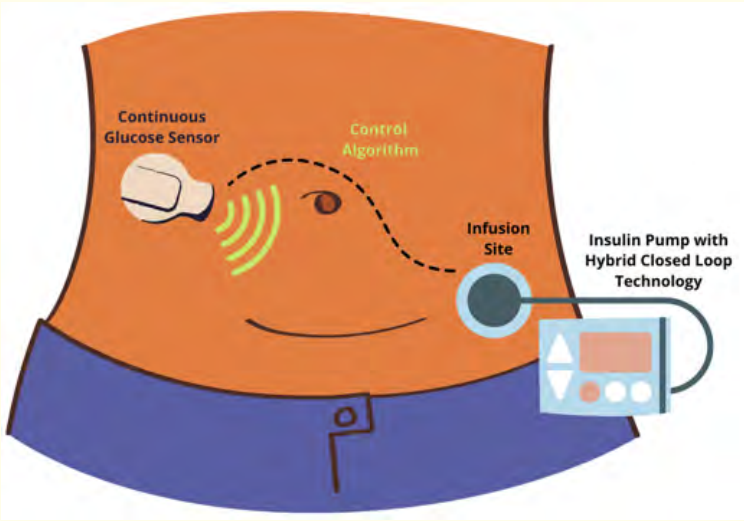


***Figure 3a:*** **This figure is for illustration purposes only. Canva was used to create this illustration.*

*Description: This is an illustration of hybrid closed-loop diabetes technology.*

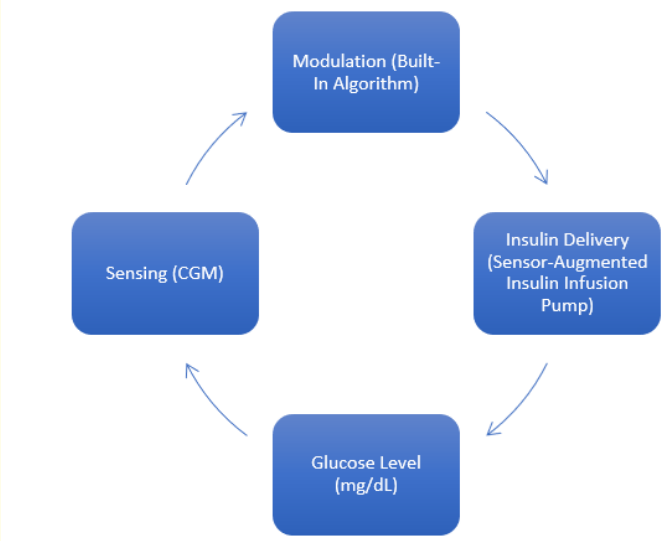


***Figure 3b:*** **Microsoft Office was used to create this illustration.*

*Description: This cycle demonstrates the how CGM and CSII work together in a HCL system.*

***Figure 3:*** *Hybrid closed-loop insulin delivery system.*

## HCL during pregnancy

The use of closed-loop technology in pregnancy was first introduced in 2011. Murphy., *et al.* conducted a study in a clinical research facility on ten women with type 1 diabetes to assess mean glucose, time in target range, hyperglycemia, and hypoglycemia through closed-loop technology [33]. During early (14.8 weeks) and late-pregnancy (28.0 weeks), glucose was continuously monitored over the course of 24 hours with the Abbott Diabetes Care FreeStyle Navigator II sensor and basal insulin was delivered through a model predictive control (MPC) algorithm [33]. During closed-loop insulin delivery, median plasma glucose levels were 117 mg/dL in early and 126 mg/dL in late pregnancy, overnight mean plasma glucose time in target range was 84% in early and 100% in late pregnancy, and overnight time in hyperglycemia was 7% in early and 0% in late pregnancy [33]. Glucose disposal was also compared at 8 weeks versus 38 weeks gestation, finding that as pregnancy progresses, glucose is disposed of less [33]. For this reason, it is recommended that women are given bolus insulin earlier and earlier as pregnancy progresses [34]. Murphy., *et al.* later published a randomized crossover pilot study that was conducted on twelve pregnant women with type 1 diabetes [35]. Patients were assigned to either closed-loop therapy, with the same CGM and MPC algorithm as their previous study, or conventional CSII for 24 hours at 19 weeks and 23 weeks gestation, with a wash out period in between [35]. Percentage of time in target range was comparable for both treatments, while time spent in hypoglycemia less than 45 mg/dL was significantly decreased during closed-loop delivery [35].

Stewart., *et al.* performed an open-label, randomized, crossover study in 2016 to compare overnight glycemic control with closed-loop therapy to sensor-augmented pump therapy, followed by a continuation phase of closed-loop therapy day and night [36]. In the closed-loop system, the FreeStyle Navigator II sensor and DANA Diabecare R Insulin Pump communicated to deliver an insulin bolus every 12 minutes through an algorithm housed on a tablet computer, and target range was set to 97 - 124 mg/dL [36]. Sixteen pregnant women between 8 and 24 weeks gestation with type 1 diabetes and a HbA1c between 6.5 and 10.0% completed 4 weeks of closed-loop therapy and sensor-augmented therapy, and fourteen of those women completed closed-loop therapy day and night until delivery [36]. In closed-

loop therapy, there was a significant decrease in mean CGM glucose both overnight ($p = 0.009$) and over a 24-hour period ($p < 0.001$), increase in time spent in target range ($p = 0.002$), and decreased in time spent in hyperglycemia ($p = 0.005$ and $p = 0.004$) [36]. Overnight, median sensor-recorded glucose values showed less variability during closed-loop therapy [36]. Stewart., *et al.* conducted another open-label, randomized, crossover trial, using the same devices as their previous study, for 28 days on sixteen pregnant women with type 1 diabetes and HbA1c between 6.5% and 10% to assess the efficacy and safety of day-and-night closed-loop insulin delivery compared to sensor-augmented pump delivery [37]. In the second phase of the study, all women continued closed-loop therapy until delivery [37]. Unlike that of their previous study, this closed-loop system had a built-in algorithm in an android mobile phone and insulin boluses were given manually 15 - 30 minutes before eating through the pump's bolus calculator [37]. Time within target glucose levels, mean glucose, and time in hyperglycemia over 140 mg/dL was comparable between both closed-loop therapy and sensor-augmented therapy [37]. In closed-loop therapy, hypoglycemic episodes and time spent in hypoglycemia in closed-loop therapy were significantly decreased ($p = 0.04$, $p = 0.02$) [37]. Less hypoglycemia (< 50 mg/dL), low blood glucose index, and nocturnal hypoglycemia, and increased overnight time in target range were observed during closed-loop therapy, although not statistically significant [37]. Women who had a HbA1c of 7.5% or less in the beginning of their pregnancy had a lower mean glucose and increased time in target range throughout the duration of their pregnancy compared to those with a HbA1c greater than 7.5%, suggesting that closed-loop therapy may have better outcomes in pregnant women who had better glucose control from the start of pregnancy [34,37].

### HCL and maternal-neonatal outcomes

Despite significant improvements in glycemic control observed in both studies published by Stewart., *et al.* there were no significant improvements observed in maternal and fetal outcomes in pregnant women on closed-loop therapy [36,37]. Combining data from both studies, study participants (N = 32) had a high rate of cesarean delivery (87.5%), preterm delivery (43.8%), large-for-gestational age (62.5%), and neonatal intensive care unit (NICU) admissions (71.9%) [34]. Of note, none of these women were using closed-loop therapy early on in pregnancy and had at least 10 to 12 weeks from time of enrollment that they were not on closed-loop therapy, which may have played a role in these outcomes [34].

## Discussion and Conclusion

Typically, patients with type 1 diabetes use insulin pumps, showing excellent glucose maintenance with their use. Upon pregnancy, many patients would prefer to continue using their insulin pump. Most patients with type 2 diabetes are not on insulin pumps, as they are either on MDI, which can be difficult to transition from, or no insulin at all, controlling their glucose through diet, exercise, or oral hypoglycemic agents. Although limited, the evidence we already have suggests CSII is successful at controlling blood glucose levels during pregnancy in women with type 1 diabetes. We can hypothesize that CSII can be useful in patients with type 2 diabetes given the great rise in insulin resistance and increased insulin requirement developed during the second and third trimester of pregnancy. Due to the increase of hPL during pregnancy, insulin resistance increases leading to more hyperglycemia. As opposed to MDI which would require multiple overnight injections, CSII can change basal and bolus insulin infusion rates at any hour of the day. As pregnancy progresses, insulin requirements increase, requiring frequent variable adjustments which can be provided by CSII pumps at any given point in time.

CGM has the most evidence-based data in the literature that suggests it is a safe, accurate device to use for measurement of glucose during pregnancy. The accuracy of CGM will allow for the decreased use of finger sticks, increasing patient compliance with treatment and subsequently improving maternal and neonatal outcomes. Sensor-augmented CSII therapy allows patients to control their insulin therapy by inputting data into insulin pumps and controlling what it gives, as there is no algorithm for insulin therapy when these devices are used separately. Mobile applications automatically send glucose data to providers who can keep track of glycemic trends day-to-day, which can ease the burden of in-person visits. This keeps the patient active in the treatment process, with a goal to help them better understand their condition and how to manage it, as patients get discouraged when they do not have a good understanding of their diabetes. At the

same time, providers are given the ability to monitor their patients' glycemic control day-to-day and make changes to treatment regimens without requiring in-person visits. CGM is not only life-changing, but can be lifesaving, as it can detect both hyperglycemic crises and hypoglycemic episodes before they happen. This gives patients time to act in their own treatment, contact their provider, or in severe cases, prevent hospitalization and even death. As women with pregestational diabetes are a high-risk population, CGM can aid their diabetes treatment and prevent complications that can arise during pregnancy.

Although hybrid closed-loop therapy has yet to be approved for pregnancy, the idea of it working successfully shows promise. Some of the goals of diabetes technology during pregnancy are to improve glucose control and increase time-in-range, of which hybrid closed-loop therapy is most successful when compared to CSII or CGM alone due to its built-in algorithm. More time spent in the target glycemic range will ultimately lead to better maternal and neonatal health outcomes. In addition, hybrid closed-loop therapy prevents overnight hypoglycemia, decreasing the risk of undetected hypoglycemia and fetal demise. More clinical studies of HCL in pregnancy and the development of a pregnancy specific algorithm adjusting for physiologic changes in each trimester are needed. Given that this system has yet to be approved by the FDA for non-pregnant patients, it will take time until we see these systems used in pregnancy.

While there is data on the use of CSII, CGM, and HCL during pregnancy there are limitations with this technology. The most important limitation to consider is the low number and small sample sizes of randomized control trials on diabetes technology in pregnant women. Observational studies have been conducted to study diabetes technology during pregnancy, however, sample sizes have been small, limiting the power of these studies. The available data on diabetes technology in pregnancy has not been shown to cause maternal or neonatal harm, however more data is needed to make a better conclusion on whether these devices can improve maternal and neonatal outcomes when compared to the tradition use of MDI. While some technology has been CE marked, the lack of evidence comparing pregnant women on diabetes technology versus control therapy (MDI) are likely why CSII and CGM have not been approved by the FDA for use in pregnancy. Most of the evidence presented in this review derives from literature published primarily on patients with type 1 diabetes, thus there is a need for more studies and a better understanding on how diabetes technology can affect pregnancy in women with type 2 diabetes.

Until wider use of CGM, CSII, and HCL, along with the development of a pregnancy specific algorithm and a proactive approach to learning more about how to manage patients on this technology, it will be a slow change to make these devices a standard of care in pregnancy. Patients themselves may be a limitation due to lack of education on how these devices work, the perception that they may be complicated to operate, and the distrust of relying on technology to manage blood glucose. Both CSII and CGM systems require the replacement of infusion sets and sensors at set intervals which may be difficult for patients to manage and lead to poor compliance. The continuous wearing of a device on the skin may not be preferred by some patients, as skin hypersensitivity, contact dermatitis, scarring from the adhesives, and lipodystrophy may occur with continued use of these devices. The devices present their own limitations as they require continuous monitoring to ensure they are operating properly without malfunction, which can be a deterrent for both patients and providers.

## Disclaimer

Continuous glucose monitoring sensors, continuous subcutaneous insulin infusion pumps, and hyper closed-loop systems are off-label and are not approved by the U.S. Food and Drug Administration for pregnancy.

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