



# Time in Range in Pregnancy: Is There a Role?

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Continuous glucose monitoring (CGM) is being used with increasing frequency as an adjunct to self-monitoring of blood glucose in pregnancy, and novel targets based on CGM data are becoming standardized. This adoption of CGM is the result of its improving accuracy, patient preference, and evolving data demonstrating associations of novel targets such as time in range (TIR) with pregnancy and neonatal outcomes. A greater understanding of the relationship of various CGM metrics to outcomes in pregnancy complicated by diabetes is needed. It is clear that TIR parameters need to be uniquely lower for pregnant women than for nonpregnant individuals. CGM technology is also an integral part of hybrid closed-loop insulin delivery systems. These insulin delivery systems will be a significant advance in the management of diabetes during pregnancy if they can achieve the pre- and postprandial targets required for pregnancy and optimize TIR.

Seventy-five years of remarkable advances in glucose monitoring have helped to elucidate the relationship of maternal glucose to adverse pregnancy and neonatal outcomes, allowed for more precise insulin dosing to achieve the target goals required to improve these outcomes, and reduced the risk of maternal hypoglycemia. Most recently, continuous glucose monitoring (CGM) is being used with increasing frequency in pregnancy, and novel targets based on CGM data are becoming standardized. Studies have demonstrated that CGM may be a useful adjunct to self-monitoring of blood glucose (SMBG) in pregnancy (1,2). Advances in CGM accuracy have allowed for progress in hybrid closed-loop insulin technology. The application of these new technologies in pregnancies complicated by diabetes will be revolutionary if the algorithms used are able to target the glucose levels necessary for pregnancy.

Outpatient monitoring of glucose in pregnancy began with urine glucose testing in 1945 with the development of Clinistest (Ames, Elkhart, IN), which allowed for a colorimetric method of measuring glucose oxidation (3). Urine glucose measurement was a poor proxy for blood glucose because of the lag in urinary glucose changes relative to blood glucose, individual variations in the threshold for renal glucose excretion, and the absence of urine glucose at the mild to moderate levels of hyperglycemia associated with poor pregnancy outcomes (4). Furthermore, urine glucose could not be used to measure hypoglycemia.

In the absence of an outpatient method of measuring blood glucose, studies of intensified care required lengthy

hospitalizations at regular intervals to regulate glucose levels with the increasing insulin doses required for pregnancy. Blood glucose was tested by fasting phlebotomy draw, followed by capillary sticks at 11:00 a.m., 3:00 p.m., and 8:00 p.m. (5,6; J. Hare, personal communication). These studies demonstrated strong associations between measures of maternal glycemia and pregnancy and neonatal outcomes in women with preexisting diabetes. Perinatal mortality (PM) was linked to average blood glucose in the last weeks of pregnancy such that average blood glucose levels >150 mg/dL had a PM rate of 23.6%; those 100–150 mg/dL had a 15.3% PM rate, and those <100 mg/dL had a 3.8% PM rate (5). Associations of maternal glucose with fetoplacental function, mode of delivery, and neonatal hypoglycemia were noted (5). Reductions in neonatal hyperbilirubinemia and respiratory distress were achieved with second- and third-trimester intensification of treatment toward euglycemia (6).

During the 1980s, home SMBG became accessible and affordable (3). SMBG with a home meter yielded results similar to standard hospitalization protocols (7). Efforts to optimize diabetes control through SMBG were found to be associated with improved outcomes (8). Mean capillary glucose levels <110 mg/dL were associated with reductions in macrosomia, respiratory distress, and neonatal hypoglycemia (9). Correlations were found between mean capillary glucose values and third-trimester A1C (9).

A1C, which provided a longer-term assessment of glycemia, was also an important advance. In 1981, elevations of A1C were found to be associated with a higher risk of congenital malformations (10). A test for A1C, performed early in

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pregnancy, estimates glycemia during organogenesis and provides a valuable assessment of the risk of congenital malformations, which increases exponentially with increasing A1C (11). Early-pregnancy A1C continues to be the gold-standard glycemic measurement used to determine the risk of birth defects. Because malformations are known to occur before the seventh week of gestation (12) and before most women realize they are pregnant, the importance of optimizing glycemic control before conception for women with preexisting diabetes was recognized. Intensification of treatment for diabetes control early in pregnancy was too late to prevent congenital malformations (13). However, studies of preconception care have demonstrated marked reductions in congenital malformations (14–16), and contraception is crucial to achieving preconception glycemic goals (17).

Of the three most common forms of diabetes in pregnancy (18), gestational diabetes mellitus (GDM) is the most common. Its prevalence depends on ethnicity/country and diagnostic testing method (19). Adverse pregnancy outcomes in women with GDM occur at a significantly higher rate than in women without diabetes (20). However, pregnancies complicated by preexisting type 1 or type 2 diabetes have even greater risks of adverse outcomes, including cesarean delivery, early delivery, maternal hypertensive complications, neonatal infection, macrosomia, respiratory complications, and birth defects, than those with GDM. Total mean costs are highest for patients with type 1 diabetes, followed by those with type 2 diabetes, and then those with GDM (21). Glycemic targets may be readily achievable in patients with GDM but are more challenging in those with type 2 diabetes and most challenging in those with type 1 diabetes, who have a greater potential for both hypoglycemic coma and diabetic ketoacidosis (22). Understandably, the majority of the work done to date on CGM in pregnancy has focused on the population with type 1 diabetes.

### **Glycemic Targets in Pregnancy**

The American Diabetes Association's (ADA's) current recommended glucose targets for the preconception and prenatal periods are shown in Table 1. To achieve these targets, current practice requires SMBG to assess day-to-day glycemic patterns and determine the need for changes in basal or bolus insulin. Assessment of fasting, premeal, and overnight glucose levels helps to determine basal insulin dosing. Postprandial blood glucose patterns determine the appropriateness of mealtime insulin boluses. SMBG testing is required before and after three meals per day for women with preexisting diabetes and fasting and after three meals per day for those with GDM. Patients with type 1 diabetes have greater fluctuations in blood glucose because of their marked insulin deficiency and may require additional testing, including nocturnal assessments, to monitor for

hypoglycemia. Usually, 2–3 days of SMBG data are required to determine trends in blood glucose levels before adjusting insulin doses.

The ADA's 2008 standards of care for preexisting diabetes in pregnancy, described in Table 1, were based on cohort studies aimed at optimizing infant body composition in type 1 diabetes (23–26). The current ADA and American College of Obstetricians and Gynecologists (ACOG) glycemic targets, also described in Table 1, are based on a 1995 study of 66 women with insulin-requiring GDM who were randomized to management based on either premeal or postprandial glucose monitoring, with fasting glucose monitored in both groups (27). Therapeutic ranges were preprandial values of 60–105 mg/dL (3.3–5.9 mmol/L) or postprandial values <140 mg/dL (7.8 mmol/L). This study demonstrated that postprandial, rather than preprandial, blood glucose monitoring improved glycemic control and decreased the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery. A similar randomized controlled trial (RCT) of premeal versus postprandial monitoring using the same therapeutic glucose ranges found reductions in preeclampsia and neonatal skinfold thickness in 61 pregnancies complicated by preexisting diabetes (28).

A 2016 Cochran review (29) examined RCT evidence from three studies of very tight, tight, moderate, and loose categorization of fasting glucose control, which corresponded to approximately <5, <6, <7, and <9 mmol/L (<90, <108, <126, and < 162 mg/dL), respectively, in pregnancies complicated by type 1 diabetes. Although the optimal fasting target could not be determined for the <7 mmol/L [<126 mg/dL] categories, there was some evidence of increased preeclampsia, caesarean delivery, and birth weight >90th percentile for “loose” control >7 mmol/L. Postprandial targets could not be evaluated because of heterogeneity. These studies were limited by small size and nonblinding of outcome data and do not sufficiently guide optimal glucose goals.

Normative data in pregnancy pooled from studies of CGM and SMBG have been reported (Table 2) and may help inform glucose targets (30). Future work focused on the use of CGM in pregnancy may further define normal glycemia in pregnancy.

### **Accuracy of CGM Systems and Glucose Meters in Pregnancy**

Various CGM systems have been studied in pregnancy. Some are blinded, meaning that the data are recorded but not immediately visible to patients; these systems are downloaded periodically for review by their provider. Some systems are intermittently scanned (iCGM), meaning that the data are available to patients, but patients must scan the device with a smartphone or handheld device to retrieve it.

**TABLE 1** Recommended Glycemic Targets for Preconception and Pregnancy

	Preconception, mg/dL (mmol/L)	Pregnancy, mg/dL (mmol/L)		
	ADA 2004 (78)*	ADA 2008 (79)*	ADA 2020 (59)†	ACOG (80)†
Fasting	80–110 (4.4–6.1)	60–99 (3.3–5.5)	<95 (<5.3)	<95 (<5.3)
1-hour postprandial			<140 (<7.8)	<140 (<7.8)
Peak postprandial		100–129 (5.6–7.2)		
2-hour postprandial	100–155 (5.6–8.6)		<120 (<6.7)	<120 (<6.7)

\*Preexisting diabetes. †Preexisting diabetes and GDM.

Other systems are real-time (rtCGM), meaning that they constantly read and display glucose levels and can sound alarms to indicate glycemic highs or lows. Only rtCGM devices have the ability to alert patients to take preemptive action to head off predicted impending hypoglycemia.

The accuracy of glucose meters and CGM devices may be assessed by several different standards (31). The International Organization for Standardization requires that meter-derived glucose values fall within  $\pm 15$  mg/dL of the comparison method for glucose levels  $\leq 100$  and  $>100$  mg/dL for at least 95% of measurements (sometimes referred to as %15/15). CGM accuracy is expected to fall within  $\pm 20$  mg/dL for the same glucose levels for  $>90\%$  of measurements (%20/20).

Mean absolute relative difference (MARD) analysis is used to describe the accuracy of CGM systems but also may be applied to blood glucose meters. MARD is calculated by averaging the absolute values of relative differences between the CGM device or meter being evaluated (A) and a reference measurement of high accuracy (B) and reported as a percentage such that the corresponding comparison method results in  $|A-B|/B \times 100\%$ . CIs are narrowed (improved) for MARD when an adequate number of paired samples have been tested (32). Glucose meter MARD scores vary, but the top seven meters achieve scores of 5.6–8.2% (33). Current accuracy scores for CGM devices when used in nonpregnant individuals include Dexcom G6 %20/20 92.5%, MARD 9.8% (34); FreeStyle Libre 14-day MARD 9.4% (35);

and FreeStyle Libre 2, MARD 9.2% (36) without calibration requirements; and Medtronic Guardian CGM MARD 9.6% with abdominal and 8.7% with arm sensor insertion sites, and a calibration requirement of three to four times daily (37).

In the narrow target ranges that are required during pregnancy, the accuracy of CGM systems at the lower glucose targets is of the utmost importance to identify impending hypoglycemia when it is occurring and avoid unnecessary hypoglycemia alerts when blood glucose levels are in the target range. Studies of CGM devices when used in pregnancy demonstrate similar accuracy as when they are used in nonpregnant subjects: Dexcom G6 %20/20 92.5% and overall MARD 10.3%, although accuracy improves with sensor insertion in the upper arm (%20/20 95.9%, MARD 8.7%) compared with the abdomen or buttock (38); and FreeStyle Libre 14-day %20/20 88.1% and overall MARD 11.8% (39).

### Adoption of CGM in Pregnancy

In a cohort of 700 women, CGM use in pregnancy increased exponentially from 0 (0%) in 2004–2008 to 5 (2.2%) in 2009–2013, to 106 (39.9%) from 2014 to 2017, as accuracy improved and insurance coverage became more broadly available (40). In a 2018 analysis of 4,340 women in the T1D Exchange clinic registry, 214 (4.9%) reported that they were either pregnant or recently pregnant (<1 year) at enrollment (41). Of those women, 69% reported insulin pump use, and 34% reported CGM use, which was a higher usage rate than in women who reported having ever been pregnant (>1 year) or having never been pregnant. The popularity of CGM in pregnancy speaks to the significant improvements in quality of life it can afford users and the perceived improvement in access to data for providers, despite still-limited recommendations on how best to use it in pregnancy and limited outcomes data.

### International Consensus Recommendations on CGM Use and Targets During Pregnancy

In 2017, the International Consensus on Use of Continuous Glucose Monitoring defined and standardized CGM metrics

**TABLE 2** Normal Glucose in Pregnancy

	Glucose	
	mg/dL	mmol/L
Fasting	71 $\pm$ 8	3.9 $\pm$ 0.4
1-hour postprandial	109 $\pm$ 13	6.0 $\pm$ 0.7
2-hour postprandial	99 $\pm$ 10	5.5 $\pm$ 0.6
24-hour mean glucose	88 $\pm$ 10	4.9 $\pm$ 0.6

Data are mean  $\pm$  SD. Adapted from ref. 31.

**TABLE 3** CGM Metrics and Targets for Adults and Pregnant Adults With Type 1 Diabetes: Recommendations of the International Consensus on Time in Range (43)

CGM Metric	Standard Targets*	Pregnancy Targets
Days CGM should be worn, <i>n</i>	14	14
Time CGM should be active, %	>70	>70
Mean glucose	Personalized target†	Personalized target†
GMI	Personalized target†	Personalized target†
Glycemic variability (coefficient of variation), %	<36	<36
TAR, level 2	<5% of time >250 mg/dL (13.9 mmol/L)	–
TAR, level 1	<25% of time 181–250 mg/dL (10.1–13.9 mmol/L)	<b>&lt;25% of time &gt;140 mg/dL (7.8 mmol/L)</b>
TIR	>70% of time 70–180 mg/dL (3.9–10.0 mmol/L)	<b>&gt;70% of time 63–140 mg/dL (3.5–7.8 mmol/L)</b>
TBR, level 1	<4% of time 54–69 mg/dL (3.0–3.8 mmol/L)	<b>&lt;4% of time 54–62 mg/dL (3.0–3.4 mmol/L)</b>
TBR, level 2 (<54 mg/dL [ $<3.0$ mmol/L])	<1% of time	<1% of time

Targets were not recommended for GDM or pregnancy complicated by type 2 diabetes, as more data are needed. Bold type indicates targets that differ for pregnancy. \*Goals vary for pediatric, older, and high-risk populations. †ADA recommends an A1C <6% (<42 mmol/mol) in pregnancy or a mean glucose <126 mg/dL (7 mmol/L).

(42). These recommendations were revised and simplified in 2019 (43). The consensus panel concluded that time in range (TIR), when used as a metric of glycemic control in addition to A1C, provided “more actionable information than A1C alone.” While A1C provides an estimate of average glucose, the CGM TIR metric puts glucose in the context of patients’ glycemic variability and exposure to hypoglycemia and hyperglycemia.

This work by the consensus panel included standard metric targets for adult patients with diabetes, including in some special populations, one of which was pregnancy in women with type 1 diabetes. These targets are summarized in Table 3. Specific recommendations for pregnancy in women with type 2 diabetes or GDM are limited, as data in these populations are lacking.

The key point is that, in pregnancy complicated by diabetes, TIR has been defined as 63–140 mg/dL (3.5–7.8 mmol/L). This metric requires attention when interpreting CGM data and the ambulatory glucose profile (AGP) reports on which they are summarized, as default settings for nonpregnancy ranges need to be adjusted for pregnancy. Some, but not all, CGM systems can be adjusted. Patients and providers need to understand how to personalize those settings and recognize the limitations of some systems.

The international consensus recommendations for CGM use in pregnancy were limited by reliance primarily on one large, multicenter RCT (44) and a prospective observational study (2) assessing outcomes in pregnancies complicated by type 1 diabetes and a dearth of data in pregnancy complicated by type 2 diabetes or GDM (43).

#### *Trials of CGM Use During Pregnancy in Women With Type 1 Diabetes*

The majority of research into the use of CGM in pregnancy has focused on women with type 1 diabetes. In these studies, CGM was used as an adjunct to standard care. SMBG fasting and postprandial targets were used as part of standard care. None of the trials were RCTs comparing outcomes using CGM metrics alone versus fasting and postprandial SMBG targets. Taken together, these studies present a compelling case for the added benefits of CGM use in pregnancy complicated by type 1 diabetes. Table 4 summarizes this work.

Early work that included data from only a few intermittent weeks of either blinded (45,46) or rtCGM data (47) yielded mixed results. A 2008 trial by Murphy et al. (46) demonstrated a reduction in birth weight and macrosomia and

**TABLE 4** Summary of Trials Comparing CGM to Standard Care in Pregnancy

Study	Design	Population	Results
Murphy et al., 2008 (46)	Multicenter, open-label RCT of blinded CGM reviewed every 4 weeks vs. standard care	46 women with type 1 diabetes; 25 women with type 2 diabetes	Primary outcome: A1C at 32–36 weeks 5.8 vs. 6.4% (39.9 vs. 46.4 mmol/L) ( $P = 0.007$ )* Secondary outcomes: macrosomia: 35 vs. 60% ( $P = 0.05$ )*; no difference in mean gestational age at delivery, preeclampsia, rate of cesarean section, preterm delivery, NICU admission, or neonatal hypoglycemia
Secher et al., 2013 (47)	Single-center RCT of rtCGM worn during weeks 8, 12, 21, 27, and 33 plus standard care vs. standard care	123 women with type 1 diabetes; 31 women with type 2 diabetes	Primary outcome: LGA status 45 vs. 34% ( $P = 0.19$ ) Secondary outcomes: no difference in A1C at 33 weeks, maternal hypoglycemia, preeclampsia, preterm delivery, or neonatal hypoglycemia
Feig et al. (CONCEPTT), 2017 (1)	Multicenter, open-label RCT of rtCGM plus standard care vs. standard care	215 women with type 1 diabetes	Primary outcome: A1C at 34 weeks mean difference $-0.19\%$ , 95% CI $-0.34$ to $-0.03$ ( $P = 0.0207$ )* Secondary outcomes: TAR 27 vs. 32% ( $P = 0.0279$ )*; TIR 68 vs. 61% ( $P = 0.0034$ )*; neonatal hypoglycemia OR 0.45, 95% CI 0.22–0.89 ( $P = 0.0250$ )*; NICU OR 0.48, 95% CI 0.26–0.86 ( $P = 0.0157$ )*; LGA status OR 0.51, 95% CI 0.28–0.90 ( $P = 0.0210$ )*; birth weight percentile 92 (95% CI 68–99) vs. 96 (95% CI 84–100) ( $P = 0.0489$ ); no difference in TBR, maternal weight gain, gestational hypertension, preeclampsia, mode of delivery, maternal length of stay, preterm delivery, or macrosomia
Voormolen et al. (GlucoMOMS), 2018 (45)	Multicenter, open-label RCT of blinded CGM reviewed every 6 weeks vs. standard care	109 women with type 1 diabetes; 82 women with type 2 diabetes; 109 women with insulin-requiring GDM	Primary outcome: macrosomia 31.0 vs. 28.4% (RR 1.06, 95% CI 0.83–1.37) Secondary outcomes: preeclampsia 3.5 vs. 11.6% (RR 0.30, 95% CI 0.12–0.80)*; no difference in pregnancy-induced hypertension, HELLP syndrome, severe hypoglycemia, A1C, birth weight, LGA status, SGA status, preterm birth, neonatal mortality, birth trauma, or neonatal hypoglycemia

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**TABLE 4** Summary of Trials Comparing CGM to Standard Care in Pregnancy

Study	Design	Population	Results
Yu et al., 2014 (48)	Prospective cohort study of blinded CGM reviewed weekly for 4 weeks	340 women with GDM	<p>Primary outcomes: mean glucose 5.7 ± 0.5 vs. 5.7 ± 0.7 mmol/L (<i>P</i> = 0.253); glucose SD 0.8 ± 0.3 vs. 1.1 ± 0.4 mmol/L (<i>P</i> &lt; 0.001)*; mean amplitude of glycemic excursions 1.8 ± 0.6 vs. 2.4 ± 0.9 mmol/L (<i>P</i> &lt; 0.001)*; mean of daily differences 1.0 ± 0.2 vs. 1.2 ± 0.3 mmol/L (<i>P</i> &lt; 0.001)*; preeclampsia 3.4 vs. 10.1% (<i>P</i> = 0.019)*; primary cesarean delivery 34.7 vs. 46.6% (<i>P</i> = 0.028)*; composite neonatal outcome 27.4 vs. 49.5% (<i>P</i> &lt; 0.001)*†</p> <p>Secondary outcomes: duration of glycemia &gt;7.8 mmol/L, 0 (95% CI 0–25) vs. 60 (95% CI 0–111) minutes/day (<i>P</i> &lt; 0.001)*; duration of glycemia &lt;3.3 mmol/L, 0 (95% CI 0–0) vs. 0 (95% CI 0–25) minutes/day (<i>P</i> &lt; 0.001)*; premature delivery 4.8 vs. 11.8% (<i>P</i> = 0.024)*; birth weight percentile 66 vs. 82 (<i>P</i> &lt; 0.01)*; macrosomia 4.1 vs. 10.8% (<i>P</i> = 0.025)*; LGA status 13.7 vs. 25.8% (<i>P</i> &lt; 0.01)*; neonatal hypoglycemia 5.5 vs. 14% (<i>P</i> = 0.011)*; hyperbilirubinemia 2.7 vs. 9.7% (<i>P</i> = 0.012)*; no difference in SGA, NICU admissions, or neonatal respiratory distress syndrome†</p>
Wei et al., 2016 (49)	Open-label RCT of second- or third-trimester rtCGM vs. standard care	106 women with GDM	<p>Primary outcomes: cesarean section 60 vs. 69% (<i>P</i> = 0.370); Apgar score at 5 minutes 9.40 ± 0.56 vs. 9.49 ± 0.50 (<i>P</i> = 0.39); macrosomia 7.8 vs. 12.7% (<i>P</i> = 0.410); neonatal hypoglycemia 7.8 vs. 12.7% (<i>P</i> = 0.410); excess maternal weight gain 33.3 vs. 56.4% (<i>P</i> = 0.039)*</p>
Paramasivam et al., 2018 (50)	Open-label RCT of 3 weeks of blinded CGM vs. standard care	50 women with insulin-requiring GDM	<p>Primary outcome: A1C at 37 weeks 33 ± 4 mmol/mol (5.2 ± 0.4%) vs. 38 ± 7 mmol/mol (5.6 ± 0.6%) (<i>P</i> &lt; 0.006)*; no difference in maternal weight gain, gestational age and delivery, mode of delivery, neonatal hypoglycemia, NICU admission, median birth weight percentile, macrosomia, LGA status, or SGA status</p>

All studies compared standard of care with SMBG to CGM plus standard care. \*Statistically significant. †To convert the data shown here from mmol/L to mg/dL, multiply values by 18. HELLP, hemolysis, elevated liver enzymes, low platelet count.

lower third-trimester A1C. However, in a 2013 RCT of intermittent rtCGM in 123 pregnant women with type 1 diabetes and 31 with type 2 diabetes, Secher et al. (47) found no benefits in A1C, severe hypoglycemia, or large-for-gestational-age (LGA) status. Furthermore, in the GlucoMOMS study (45), 300 women with type 1 diabetes (*n* = 109), type 2 diabetes (*n* = 82), or GDM (*n* = 119) were randomized to either standard care or blinded CGM

reviewed every 6 weeks plus standard care. This study found no difference in the risk of the primary end point of macrosomia between the two groups. The only secondary end point to demonstrate a significant difference was a reduction in preeclampsia in the CGM group of 3.5 versus 11.6% (relative risk [RR] 0.30, 95% CI 0.12–0.80). Analysis of multiple secondary end points, including A1C and maternal and neonatal hypoglycemia,

showed no further significant differences between groups. Proponents of CGM use in pregnancy might argue that these conflicting results are unsurprising, as the true benefit of CGM use is that it enables actions to adjust for glucose in real time throughout pregnancy—something none of these studies were designed to support.

The largest study of this type to date, the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) (1), was a multicenter RCT that compared SMBG plus CGM to SMBG alone in 325 women who were either planning pregnancy ( $n = 110$ ) or who were pregnant ( $n = 215$ ). CONCEPTT demonstrated the benefit of CGM in addition to SMBG in pregnant women; it found a small but statistically significant difference in A1C of  $-0.19\%$  (95% CI  $-0.34$  to  $-0.03$ ;  $P = 0.0207$ ) in pregnant women who used CGM versus those who did not. Pregnant women using CGM had statistically significantly less time above range (TAR) than control participants without an increase in time below range (TBR) or in the number of severe hypoglycemic episodes. Perhaps most importantly, there was significant improvement in neonatal outcomes. CONCEPTT found a statistically significant lower incidence of LGA status (odds ratio [OR] 0.51, 95% CI 0.28–0.90,  $P = 0.0210$ ), a reduction in neonatal hypoglycemia (OR 0.45, 95% CI 0.22–0.89,  $P = 0.0250$ ), a 1-day reduction in hospital length of stay ( $P = 0.0091$ ), and fewer neonatal intensive care admissions (OR 0.48, 95% CI 0.26–0.86,  $P = 0.0157$ ).

### *Trials of CGM Use During Pregnancy in Women With Type 2 Diabetes or GDM*

Outcomes data for the use of CGM in type 2 diabetes and GDM are far less robust. To date, no RCTs have specifically studied its use in type 2 diabetes in pregnancy, and the data for its use in GDM are limited (Table 4).

In a 2014 prospective cohort study by Yu et al. (48) of 340 women with GDM who had 4 weeks of blinded CGM plus standard care or standard care alone, those with blinded CGM were found to have a statistically significant lower rate of preeclampsia, improvements in CGM metrics, and a lower rate of a neonatal composite that included premature delivery, macrosomia, LGA status, small-for-gestational-age (SGA) status, obstetric trauma, neonatal hypoglycemia, hyperbilirubinemia, and respiratory distress. However, participants using CGM were more likely to receive insulin than those in the standard care group (27.9 vs. 12.2%,  $P < 0.001$ ).

A 2016 rtCGM study by Wei et al. (49) found only limited benefits. They reported on 106 women with GDM who were randomized to receive standard care plus CGM for 4 or

8 weeks of their pregnancy (either 24–28 or 28–36 weeks) versus standard care with SMBG. This study found no difference in A1C or obstetric outcomes, including macrosomia, neonatal hypoglycemia, and cesarean delivery, although this finding may have resulted from the short duration of the intervention. Interestingly, more women required insulin therapy in the CGM group than in the control group (31.3 vs. 12.7%,  $P = 0.020$ ). Excessive maternal weight gain was lower in the CGM group (33 vs. 56.4%,  $P = 0.039$ ).

In a 2018 RCT of 50 women with insulin-treated GDM randomized to 3 weeks of blinded iCGM plus standard care versus standard care alone, Paramasivam et al. (50) found a lower mean A1C at 37 weeks in the CGM group compared with the control group ( $33 \pm 4$  mmol/mol [ $5.2 \pm 0.4\%$ ] vs.  $38 \pm 7$  mmol/mol [ $5.6 \pm 0.6\%$ ],  $P < 0.006$ ). Notably, 92% of the CGM group achieved the target A1C goal at 37 weeks compared with 68% of the control group ( $P = 0.012$ ).

It is unclear why these studies of blinded CGM in GDM demonstrated improved glycemic control, whereas the studies of blinded CGM use in type 1 diabetes did not. One could hypothesize that the difference in outcomes between the trials of blinded intermittent CGM use in type 1 diabetes and those in GDM could be that the level of diabetes education, attention to monitoring, and self-empowerment to adjust insulin in the type 1 diabetes population were higher at baseline, so the retrospective CGM data in GDM improved that population's understanding of their diabetes more and increased their interventions to control their glucose more than in the women in the type 1 diabetes trials.

### **Comparison of rtCGM to iCGM in Pregnancy**

There are limited data comparing differences in outcomes between continuous use of rtCGM and iCGM in pregnancy. In their observational study of 186 women with type 1 diabetes (92 using rtCGM and 94 using iCGM), Kristensen et al. (2) did not find a difference in neonatal outcomes between participants who used rtCGM compared with iCGM. In a small RCT (51), 25 pregnant women with type 1 diabetes using insulin pumps were randomized in the first trimester to either rtCGM or iCGM. Patients using rtCGM achieved lower A1C ( $6.52 \pm 1.3$  vs  $6.82 \pm 0.7\%$ ,  $P < 0.05$ ) and mean glucose ( $6.92 \pm 2.1$  vs  $7.42 \pm 3.4$  mmol/L,  $P < 0.05$ ) in the first trimester compared with those using iCGM. However, while those using rtCGM continued to have lower A1C and mean glucose in their second and third trimesters, the difference was no longer statistically significant. There was no significant difference in the rates of severe hypoglycemic events.

However, rtCGM may be more effective than iCGM at reducing TBR. Kristensen et al. (2) reported a reduction in TBR with rtCGM compared with iCGM. There are also some data in the nonpregnant adult population to support this finding. In an unmasked parallel group study by Reddy et al. (52) of 40 nonpregnant adults with type 1 diabetes who were treated with multiple daily insulin injections and had a history of hypoglycemia, participants were randomized to rtCGM or iCGM for 8 weeks. Those randomized to rtCGM were below the target range 2.4% of the time compared with 6.8% of the time for those with iCGM (median between-group difference  $-4.3\%$ ,  $P = 0.006$ ).

### Association of CGM Metrics With A1C

In an analysis of four RCTs performed in nonpregnant patients with type 1 diabetes using CGM ( $n = 545$ ), Beck et al. (53) concluded that TIR and mean glucose are highly correlated with each other but only moderately correlated with A1C and that, for a given TIR, a wide range of A1C values was possible. In this analysis, TIR (70–140 mg/dL [3.9–7.8 mmol/L]) of 70% estimated an A1C of 5.8%; however, the range of A1C this TIR percentage actually represented was 4.4–7.2%. Likewise, TIR (70–180 mg/dL [3.9–10 mmol/L]) of 70% estimated an A1C of 7.0%; however, the range of A1C this TIR actually represented was 5.6–8.3%.

Because A1C is not a direct measure of glycemia and can be affected by a number of factors, there have been calls to replace A1C with CGM metrics such as TIR or mean glucose. This recommendation makes sense, as CGM-derived mean glucose is a more accurate representation of average glucose than A1C, and TIR provides valuable information aimed at minimizing hyperglycemia, hypoglycemia, and glycemic variability that can inform management decisions. However, clinicians and patients have long placed great meaning on A1C values, which have been associated with diabetes outcomes consistently for decades, and there are still relatively few studies demonstrating that relationship with CGM metrics.

This situation has led to various CGM-derived estimations of A1C, such as the glycemic management indicator (GMI), that are based on different calculations of mean glucose in nonpregnant adults. The use of these metrics in pregnancy is problematic, as A1C is known to be significantly lower during pregnancy for a variety of reasons (54). This difference has led to the proposal of a pregnancy-specific estimated average glucose calculation; however, this proposal has not gained widespread acceptance because it is not part of the standard AGP report, of which GMI is a component.

### Association of CGM Metrics With Pregnancy and Neonatal Outcomes

To date, there are no RCTs comparing either different CGM metrics (e.g., mean glucose vs. TIR) or different targets for CGM metrics (e.g., mean glucose 120 vs. 130 mg/dL [6.7 vs. 7.2 mmol/L]) in pregnancies complicated by diabetes. However, there are some data associating CGM metrics with outcomes.

In the 2019 study by Kristensen et al. (2), CGM data were analyzed by trimester in an observational cohort of 186 pregnancies complicated by type 1 diabetes (Table 5). In the first trimester, there was no statistically significant difference in TIR, TAR, TBR, mean glucose, or glucose SD between pregnancies with LGA status and those without. However, A1C was 0.3% (3.7 mmol/mol) higher in the groups with LGA versus without LGA status. In the second and third trimesters, LGA status was associated with higher A1C, mean glucose, and TAR, and lower TIR and TBR. The study found similar associations with a composite of neonatal outcomes that included macrosomia, shoulder dystocia, neonatal hypoglycemia, or admission to the neonatal intensive care unit (NICU) for  $>24$  hours. Outcomes were adjusted for maternal age, smoking status, early-pregnancy BMI, and CGM device. Importantly, the mean maternal glucose observed in the LGA group in the third trimester was 0.5 mmol/L (9 mg/dL) higher than in the no-LGA group with an adjusted OR of 1.57 (95% CI 1.12–2.19,  $P < 0.001$ ). The mean TIR was 4.6% lower in the LGA group than in the no-LGA group with an adjusted OR of 0.97 (95% CI 0.95–1.00,  $P = 0.04$ ). The coefficient of variation (glycemic variability measure) was not associated with LGA status.

In a retrospective study of 41 pregnant women with type 1 diabetes using CGM in addition to SMBG, Mulla et al. (55) did not find a relationship between first-, second-, or third-trimester CGM glycemic variability, mean glucose, or A1C with fetal abdominal circumference percentile, estimated fetal weight percentile, or birth weight, except for an association of first-trimester mean glucose with estimated fetal weight percentile. TIR was not an available metric. Accelerated fetal abdominal circumference percentile growth was noted between 26 and 32 weeks.

In a prospective, observational study of 162 women with GDM (56), mean glucose was significantly higher in pregnancies complicated by LGA status (6.2 vs. 5.8 mmol/L [111.6 vs. 104.4 mg/dL],  $P = 0.025$ ). Neither TIR nor glycemic variability were associated with LGA status. Functional data analysis demonstrated that mean glucose was significantly higher overnight in pregnancies complicated by LGA status versus those without this complication ( $6.0 \pm 1.0$  mmol/L [108.0  $\pm$  18 mg/dL] vs.  $5.5 \pm 0.8$  mmol/L [99.0  $\pm$  14.4 mg/dL],  $P = 0.005$ ).



**TABLE 5** Analysis of Adjusted CGM Variables Tested for Associations With LGA Status

Variable	LGA (n = 98)	No LGA (n = 88)	Adjusted OR (95% CI)	P
<i>First trimester</i>				
A1C, mmol/mol	54.1 ± 1.0	50.4 ± 9.5	1.04 (1.00-1.08)	0.02*
A1C, %	7.1 ± 1.0	6.8 ± 0.9	—	—
Mean glucose, mmol/L	7.9 ± 1.3	7.7 ± 1.5	1.16 (0.19-1.49)	0.24
SD, mmol/L	3.2 ± 0.8	3.2 ± 0.9	1.09 (0.73-1.62)	0.67
Coefficient of variation, %	40.5 ± 7.2	40.6 ± 7.3	0.99 (0.95-1.04)	0.77
TIR, %†	48.2 ± 13.6	51.9 ± 14.5	0.98 (0.95-1.00)	0.07
TAR, %	44.8 ± 14.6	40.9 ± 16.3	1.02 (1.00-1.04)	0.07
TBR, %	7.0 ± 5.1	7.2 ± 5.0	0.98 (0.92-1.05)	0.60
<i>Second trimester</i>				
A1C, mmol/mol	46.4 ± 7.4	43.7 ± 8.3	1.05 (1.01-1.10)	0.02*
A1C, %	6.4 ± 0.7	6.1 ± 0.8	—	—
Mean glucose, mmol/L	7.6 ± 1.0	7.1 ± 1.3	1.53 (1.12-2.08)	<0.001*
SD, mmol/L	2.9 ± 0.6	2.7 ± 0.7	1.65 (1.00-2.74)	<0.05*
Coefficient of variation, %	37.8 ± 5.9	37.7 ± 6.7	1.00 (0.95-1.06)	0.93
TIR, %†	51.8 ± 12.3	57.9 ± 14.4	0.96 (0.94-0.99)	<0.01*
TAR, %	41.9 ± 12.8	34.0 ± 15.9	1.04 (1.02-1.07)	<0.001*
TBR, %	6.4 ± 4.5	8.0 ± 5.7	0.93 (0.87-0.99)	0.02*
<i>Third trimester</i>				
A1C, mmol/mol	47.2 ± 6.7	44.0 ± 8.2	1.06 (1.02-1.11)	<0.01*
A1C, %	6.5 ± 0.6	6.2 ± 0.8	—	—
Mean glucose, mmol/L	7.3 ± 1.1	6.8 ± 1.1	1.57 (1.12-2.19)	<0.001*
SD, mmol/L	2.6 ± 0.6	2.5 ± 0.6	1.60 (0.92-2.77)	0.09
Coefficient of variation, %	35.9 ± 5.5	36.1 ± 6.2	0.99 (0.94-1.05)	0.84
TIR, %†	57.6 ± 12.8	62.2 ± 13.4	0.97 (0.95-1.00)	0.04*
TAR, %	37.0 ± 13.5	30.2 ± 15.3	1.03 (1.01-1.06)	<0.01*
TBR, %	5.4 ± 4.4	7.6 ± 6.4	0.92 (0.86-0.98)	<0.01*

Adjusted for age, smoking status, BMI, and CGM device. Data in LGA and non-LGA columns are mean ± SD. \*Statistically significant. †TIR 63–140 mg/dL (3.5–7.8 mmol/L). Adapted from ref. 2.

In a 2015 analysis of CGM data from two previously published studies with a total of 117 pregnant participants (89 with type 1 diabetes and 28 with type 2 diabetes), Law et al. (57) found that mean glucose in each trimester was associated with LGA status, whereas TIR was associated with LGA status only in the second trimester.

In a further analysis of data from CONCEPTT, Scott et al. (58) used functional data analysis to assess differences in glucose temporal patterns between CGM users and SMBG users,

insulin pump users and those on a multiple daily injection regimen, and those with pregnancies complicated by LGA status versus those without this complication. This analysis demonstrated that women with pregnancies complicated by LGA status had significantly higher glucose levels for 4.5 hours/day in the first trimester, 16 hours/day in the second trimester, and 14 hours/day in the third trimester than those without the LGA complication. The analysis further demonstrated periods of higher glucose primarily during the day that were not obvious from standard glucose metrics.

## Future Work

National recommendations on the use of CGM in pregnancy vary, but many support its use in type 1 diabetes (59–61). Further work is needed to demonstrate its value in type 2 diabetes and GDM. In 2019, the International Consensus on Time in Range (43) acknowledged the need for additional work, stating that “to fundamentally change clinical care with use of the new metrics, it would be important to demonstrate the metrics relate to and predict clinical outcomes.” Many questions also remain on how to use CGM technology to the greatest benefit during pregnancy.

### *Should CGM Targets for GDM and Type 2 Diabetes Vary From Those for Type 1 Diabetes?*

This question needs further study. Mean glucose levels in normal pregnancies are considerably lower than targets applied for pregnancies complicated by diabetes. RCTs aimed at studying normal-range glucose targets may be more feasible in pregnancies complicated by GDM and type 2 diabetes than in those in women with type 1 diabetes.

### *Should TIR or Mean Glucose Replace A1C?*

Our understanding of the optimal use of and targets for CGM metrics in type 1 diabetes and pregnancy is still evolving. In CONCEPTT, did the addition of CGM improve neonatal outcomes because of improved adherence to fasting and postprandial targets and therefore A1C or because it introduced the measures of TIR, glycemic variability, or both? Which CGM metrics are most important in predicting specific outcomes?

TIR and mean glucose are highly correlated with each other. Every 5% increase in TIR is associated with an improvement in neonatal outcomes (62), but mean glucose may be more predictive of LGA status. However, TBR should be avoided for maternal well-being. It is possible that, over time, mean glucose will replace A1C as the long-term hyperglycemia exposure metric associated with pregnancy and neonatal outcomes, and a goal of higher TIR and lower TBR may be used as an additional metric to reduce maternal hypoglycemia and possibly improve quality of life and reduce diabetes distress.

### *Should TIR or Mean Glucose Replace Pre- and Postprandial Glucose Targets?*

Neither TIR nor mean glucose should replace pre- and postprandial targets. Pre- and postprandial glucose patterns are the basis for evidence-based adjustments of basal and

bolus insulin doses. Neither TIR nor mean glucose provide the necessary level of granularity for this purpose.

### *With CGM Metrics, Are We Able to Optimize Neonatal Outcomes?*

Despite evidence for improvements in LGA status and macrosomia in the CGM arm of CONCEPTT (1), 53% of infants in the CGM arm were classified as having LGA status, 23% had macrosomia, and 15% experienced neonatal hypoglycemia. We need greater understanding of optimal glycemic targets in pregnancy complicated by diabetes, as well as of nonglucose mediators of fetal growth.

### *What Is the Relationship Between Temporal Variation in Glycemia Seen in Functional Data Analysis and the Underlying Pathophysiology of Adverse Pregnancy and Neonatal Outcomes?*

As previously mentioned, a 2015 functional data analysis of CGM data from 117 women with diabetes (89 with type 1 diabetes and 29 with type 2 diabetes) who had participated in either of two RCTs of CGM use in pregnancy demonstrated higher daytime glucoses patterns in pregnancies that resulted in an LGA infant (57). However, nocturnal hyperglycemia was associated with LGA status in GDM (56). More work is needed to understand the relationship between temporal variations in glycemia and the underlying pathophysiology of adverse outcomes.

### *Should a CGM Metric Incorporating Temporal Glycemic Variation Be Adopted?*

More study is needed to follow up on recently published data on the role of temporal glycemic variation in affecting pregnancy and neonatal outcomes.

### *What Is the Relationship Between CGM Metrics and Temporal Glycemic Variations and the Normal Physiology of Pregnancy?*

The GOMOMS (Glycemic Observation and Metabolic Outcomes in Mothers and Offspring) study, a prospective, observational study designed to characterize maternal glucose over the course of pregnancy using CGM and oral glucose tolerance testing data, may help to answer this question (63).

### *What Is the Cost-Benefit Ratio of CGM Use in Pregnancy?*

A financial model by the CONCEPTT collaborative predicted significant cost savings with CGM use in pregnant women with type 1 diabetes. The model was based on the U.K. National Health Service structure and estimated an annual cost of care for such pregnancies nationally of

£23,725,648 (USD \$30,843,342) compared with £14,165,187 (USD \$18,414,743) with universal CGM use during pregnancy in women with type 1 diabetes (64). Obviously, more work is needed in this area, both based on a U.S. care model and in patients with either type 2 diabetes or GDM.

### *What Is the Role of Hybrid Closed-Loop Insulin Delivery Systems in Pregnancy?*

More data on the use of insulin pumps in pregnancy are critically needed. Although many practitioners and patients prefer to use insulin pumps in pregnancy complicated by type 1 diabetes, early work looking at the use of pumps has had mixed results (44,65–68). Given the progressive increase in insulin requirement during pregnancy (69), this state seems like the ideal one in which to demonstrate a benefit in glycemic control with a CGM-enabled hybrid closed-loop (HCL) insulin delivery system. To date, the data on HCL insulin delivery for pregnant women are limited to two small studies in women with type 1 diabetes (70,71).

### Conclusion

To date, optimal glycemic control in pregnancy has aimed to reduce adverse pregnancy and neonatal outcomes by lowering average glucose, as represented by A1C, while minimizing maternal hypo- and hyperglycemia. CGM provides a powerful new tool that promises to help achieve the goals of improved outcomes in multiple ways.

The first is by potentially providing a more accurate representation of mean blood glucose. A1C has been used for decades as a proxy for mean blood glucose, and pregnancy outcomes are strongly associated with A1C. The ADA recommends an A1C <6% (42 mmol/mol) in pregnancy. This recommendation is based on multiple studies in pregnant women with type 1 diabetes, type 2 diabetes, or GDM, demonstrating the strong relationship of A1C to maternal and neonatal outcomes (12,72–77). There are strong arguments that CGM-derived mean (interstitial) glucose may provide a more accurate representation of mean blood glucose than A1C, both in and out of pregnancy. If A1C were to be replaced by a more accurate CGM metric, one would assume that the CGM metrics most representative of mean blood glucose (i.e., mean glucose) would be the most closely associated with diabetes complications. However, accuracy currently limits CGM use in pregnancy because CGM systems are less accurate than the best meters and therefore should be used only as an adjunct to meter glucose testing. CGM accuracy may continue to improve with ongoing innovation. To date, no group has provided specific recommended CGM targets for mean glucose in pregnancy.

The second way in which CGM may improve glycemic management during pregnancy is by the introduction of TIR as a new metric to be used in addition to some estimation of mean blood glucose. TIR is especially valuable in patients with type 1 diabetes and those with risk factors for severe hypoglycemia. By definition, more time spent in the target range indicates less time spent in the undesirable below- and above-target ranges. CONCEPT demonstrated that an increasing percentage of TIR is associated with improved outcomes. However, the proposed TIR target of 63–140 mg/dL (3.5–7.8 mmol/L) does not distinguish between optimal overnight/fasting/preprandial glucose targets and postprandial glucose targets that are necessary for data-driven basal and bolus insulin adjustments, respectively, that are required throughout pregnancy. For example, although meeting the TIR target, CGM glucose levels of 140 mg/dL (7.8 mmol/L) overnight and 1-hour postprandial glucose levels of 63 mg/dL (3.5 mmol/L) are both unacceptable. Thus, TIR cannot be used as a stand-alone metric.

The third contribution of CGM to diabetes management during pregnancy, and the one that perhaps accounts for its popularity with patients and providers, is the improvement in patient experience (e.g., resulting from a reduced need for SMBG and reductions in hypoglycemia and hyperglycemia) and provider experience (e.g., resulting from increased ease of access to better and more standardized data).

A fourth benefit, and perhaps the most important for neonatal outcomes, is that CGM provides far more data and therefore more opportunities to improve glucose than SMBG alone. Patients are empowered to manage their glucose levels, since more data are easily presented to them. As HCL insulin delivery systems continue to evolve, CGM will become even more important as an integral part of that technology. Some CGM-enabled HCL systems now have algorithms that achieve the overnight and preprandial glucose targets that guidelines recommend. A further innovation in CGM technology would be to identify optimal TIR for postprandial periods separately from overnight and preprandial periods, allowing for the achievement of even tighter glycemic control. Again, much work is needed.

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### DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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