# Continuous Glucose Monitoring in Pregnancy: We Have the Technology but Not All the Answers

Huge progress has been made in the management of pregnant women with type 1 diabetes. With increasing recognition of the importance of good glycemic control (before and during pregnancy) and improvements in obstetric and neonatal care, the vast majority of women with diabetes can expect to deliver a healthy live-born infant. However, the problem of macrosomia, present in the era after insulin was first introduced (1), persists, as highlighted in recent reports from Scandinavia (2,3). Near-optimal glucose control, defined as $HbA_{1c} \leq 7.0\%$ (53 mmol/mol) in the nonpregnant state, does not prevent neonatal morbidity (macrosomia, preterm delivery, neonatal hypoglycemia) (4). The U.K. National Institute for Health and Care Excellence (NICE) now recommends more stringent glucose control targets, with an $HbA_{1c} < 6.1\%$ (43 mmol/mol) throughout pregnancy (5). However, the dilemma of how best to balance the daily risk of maternal hypoglycemia with the longer-term risks of the effect of hyperglycemia to the fetus remains.

In this issue of *Diabetes Care*, Secher at al. (6) report on their results from a randomized controlled trial of intermittent real-time continuous glucose monitoring (CGM) in pregnant women with diabetes. They included 154 pregnant women (123 with type 1 diabetes, 31 with type 2 diabetes) randomized to either real-time CGM or routine capillary glucose monitoring. Women in both groups were advised to perform at least seven finger-stick tests daily (before and after meals and before bed). The CGM group was advised to use real-time CGM for at least 6 days at 8, 12, 21, 27, and 33 weeks' gestation. Women's concern about allocation to the CGM arm was identified as a key barrier to recruitment and sensor compliance was poor. Only 49 out of 76 women (64%) reported using CGM as per protocol, and near continuous sensor use (at least 60% of the time) was chosen by only 5 women (7%). There was no difference in maternal glucose control ($HbA_{1c}$ or capillary glucose levels) or neonatal outcomes (macrosomia, preterm delivery, or neonatal hypoglycemia) between the two groups, either on the intention-to-treat or per-protocol analysis. The authors concluded that intermittent use of real-time CGM did not improve glycemic control or neonatal morbidity in this cohort of pregnant women.

Women in this study had good glycemic control throughout pregnancy. The baseline $HbA_{1c}$ 6.7% (50 mmol/mol) improved to 6.1% (43 mmol/mol) at 33 weeks. Still, neonatal morbidity was high, with 40% of infants being macrosomic and 25% of infants being delivered preterm or treated for hypoglycemia. The CGM had no apparent benefits on glucose control (hyper or hypoglycemia) or neonatal outcomes, either in multiple daily injection or insulin pump users. Secher et al. focused primarily on prevention of nocturnal hypoglycemia. Alarms were activated for hypoglycemia (interrupting sleep in one-third of CGM users). There were seven episodes of severe hypoglycemia during CGM, confirming previous reports that CGM use is only weakly related to hypoglycemia exposure (7).

An advantage, as well as a pitfall, for diabetes technology researchers is the speed with which technology evolves. In the case of CGM, new improved sensors are anticipated approximately every 2 years. Even with older, less accurate CGM the suboptimal compliance is surprising and unexpected. In contrast to insulin pump therapy, which is often associated with an improved quality of life, CGM can be burdensome, with qualitative data suggesting that for these women the CGM burdens (discomfort, sensor inaccuracy, sleep disturbances) outweighed the potential benefits (8).

The current results are in contrast to our own previous retrospective CGM study, which found benefits on maternal glucose control (in late gestation) and neonatal birth weight (9). Our CGM intervention focused primarily on reducing postprandial hyperglycemia. Because the CGM data were blinded, women were unburdened by alarms or sensor inaccuracy, which may have assisted compliance. Baseline maternal $HbA_{1c}$ levels were higher (mean 7.3% or 56 mmol/mol), which made it easier to achieve further improvement. A meta-analysis of real-time CGM outside of pregnancy (7) identified two key predictors for maximal $HbA_{1c}$ reduction: baseline $HbA_{1c}$ and duration of sensor use. It now seems that near-continuous sensor use (6–7 days per week) and higher baseline $HbA_{1c}$ ($\geq 7\%$) are required. A further methodological limitation should be noted. The primary outcome in the current trial was macrosomia, an outcome usually associated with maternal hyperglycemia (10,11). Interventions aiming to reduce macrosomia should focus primarily on reducing hyperglycemia rather than minimizing hypoglycemia. Women in this trial still had 25% of capillary glucose readings above 8 mmol/L (144 mg/dL), with hyperglycemia presumably occurring most frequently after meals. CGM without carbohydrate-based insulin algorithms and/or regular dietary input may have been inadequate for optimal postprandial glucose control.

Throughout pregnancy, fine tuning of dietary intake and prandial insulin boluses is required to achieve stringent postmeal glucose targets without hypoglycemia. The dose and optimal timing of each prandial bolus is complicated, depending on the macronutrient content of the meal (carbohydrate quantity, glycemic index, and protein and fat concentration), ambient glucose and plasma insulin concentration, and highly variable insulin pharmacokinetics. Even outside pregnancy, the time to peak plasma insulin of "fast-acting" insulin analogs (Aspart and Humalog) ranges from 30–110 min (12). As pregnancy advances, the physiological changes of increased insulin resistance, delayed glucose disposal, and slower insulin absorption (mean time to peak plasma insulin of 80 ± 30 min in late pregnancy) all contribute to ensuring a steady but surplus to the required supply of glucose to the fetus (13).

The use of CGM in pregnancy may hold its greatest potential in assisting prandial insulin and dietary decisions.

For clinicians hoping that CGM may help to improve maternal/fetal outcomes, the current results are disappointing. Acceptance of, and compliance with, CGM in unselected pregnant women was poor. It is also possible that intermittent use of real-time CGM is not beneficial. Clearly, more data are required before routine clinical use of CGM in pregnancy can be fully endorsed. An international Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) will now evaluate the role of continuous real-time CGM before and during pregnancy. It is not the devices per se but how patients, their spouses/significant others, and health professionals interact with CGM that will likely determine outcomes. At this point in time we have the technology, but we don't have all the answers.

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**References**

1. Nothmann M. Diabetes mellitus and pregnancy. N Engl J Med 1941;224:275–280
2. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. Diabetes Care 2009;32:2005–2009
3. Klemetti M, Nuutila M, Tikkanen M, Kari MA, Hiilesmaa V, Teramo K. Trends in maternal BMI, glycaemic control and perinatal outcome among type 1 diabetic pregnant women in 1989-2008. Diabetologia 2012;55:2327–2334
4. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia 2002;45:1484–1489
5. NICE guideline 63: Diabetes in pregnancy: management of diabetes and its complications in pregnancy from the pre-conception to the postnatal period [article online], 2008. Available from www.nice.org.uk. Accessed 1 February 2013
6. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care 2013;36:1877–1883
7. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805
8. Secher AL, Madsen AB, Ringholm L, et al. Patient satisfaction and barriers to initiating real-time continuous glucose monitoring in early pregnancy in women with diabetes. Diabet Med 2012;29:272–277
9. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008;337:a1680
10. Kerssen A, de Valk HW, Visser GH. Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. Diabetes Care 2007;30:1069–1074
11. Herranz L, Pallardo LF, Hillman N, Martin-Vaquero P, Villarroel A, Fernandez A. Maternal third trimester hyperglycaemic excursions predict large-for-gestational-age infants in type 1 diabetic pregnancy. Diabetes Res Clin Pract 2007;75:42–46
12. El-Khatib FH, Russell SJ, Nathan DM, Sutherlin RG, Damiano ER. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010;2:27ra27
13. Murphy HR, Elleri D, Allen JM, et al. Pathophysiology of postprandial hyperglycaemia in women with type 1 diabetes during pregnancy. Diabetologia 2012;55:282–293