Intensive Glycemic Treatment During Type 1 Diabetes Pregnancy: A Story of (Mostly) Sweet Success!

Helen R. Murphy

Diabetes Care 2018;41:1563–1571 | https://doi.org/10.2337/dci18-0001

Studies from Scotland and Canada confirm large increases in the incidence of pregnancies complicated by pregestational type 1 diabetes (T1D). With this increased antenatal workload comes more specialization and staff expertise, which may be important as diabetes technology use increases. While euglycemia remains elusive and obstetrical intervention (earlier delivery, increased operative deliveries) is increasing, there have been some notable successes in the past 5–10 years. These include a decline in the rates of congenital anomaly (Canada) and stillbirths (U.K.) and substantial reductions in both maternal hypoglycemia (both moderate and severe) across many countries. However, pregnant women with T1D still spend ∼30–45% of the time (8–11 h/day) hyperglycemic during the second and third trimesters. The duration of maternal hyperglycemia appears unchanged in routine clinical care over the past decade. This ongoing fetal exposure to maternal hyperglycemia likely explains the persistent rates of large for gestational age (LGA), neonatal hypoglycemia, and neonatal intensive care unit (NICU) admissions in T1D offspring. The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) found that pregnant women using real-time continuous glucose monitoring (CGM) spent 5% less time (1.2 h/day) hyperglycemic during the third trimester, with clinically relevant reductions in LGA, neonatal hypoglycemia, and NICU admissions. This article will review the progress in our understanding of the intensive glycemic treatment of T1D pregnancy, focusing in particular on the recent technological advances in CGM and automated insulin delivery. It suggests that even with advanced diabetes technology, optimal maternal dietary intake is needed to minimize the neonatal complications attributed to postprandial hyperglycemia.

Prospective nationwide studies confirm that despite widespread suboptimal glycemic control, the majority of women with pregestational type 1 diabetes (T1D) deliver live-born babies (1,2). While complications attributed to maternal hyperglycemia throughout pregnancy—namely, rates of large for gestational age (LGA), preterm delivery, and neonatal intensive care unit (NICU) admissions—remain high, almost 95% of women with T1D leave hospital with a live-born infant. A large population-based study from the U.K. reported a consistent reduction in stillbirths, from 25.8 to 10.7 per 1,000 births, in women with pregestational diabetes over the past decade (3). The absolute risk of stillbirth in T1D is now 10–13 per 1,000 births, which although higher than the background maternity population risk of <5 per 1,000, is an important success. A Canadian study reported a 23% decline in the rates of congenital anomaly but without improvement in perinatal mortality (4). In contrast, a contemporary study from Scotland found no improvements in stillbirth or perinatal mortality rates for women with diabetes (5). Both the Canadian and Scottish studies describe significant increases

Norwich Medical School, University of East Anglia, Norwich, U.K.
Wolfson Diabetes and Endocrine Clinic, Cambridge University Hospitals NHS Foundation Trust, Cambridge, U.K.
Department of Women & Children's Health, King's College London, London, U.K.
Corresponding author: Helen R. Murphy, hm386@medschl.cam.ac.uk.

Received 5 February 2018 and accepted 12 February 2018.

See accompanying articles, pp. 1572 and 1579.

in the incidence of pregnancies complicated by pregestational diabetes over the past 15 years (a doubling in Canada, and a 44% increase in T1D and a 90% increase in T2D in Scotland) (4,5).

The reasons for the U.K. reductions in stillbirths are most likely multifactorial, including, for example, improvements in the provision and uptake of prepregnancy care, tighter glycemic targets (HbA_{1c} <6.5% [48 mmol/mol]), and increased specialization of antenatal diabetes care. Over the past 15 years, the number of specialist diabetes maternity clinics has decreased (from 231 to 155), while the incidence of pregnancies complicated by pregestational diabetes has increased. This means that there are now twice as many women with pregestational diabetes per clinic. Balanced with the increased antenatal clinic workload is a more focused concentration of staff expertise, which may be important as diabetes technology becomes more complex. It also means a need for more efficient antenatal diabetes care provision.

Current antenatal diabetes care pathways involve frequent clinic visits with an obstetrician, endocrinologist, diabetes educator, diabetes specialist midwife, or diabetes dietitian typically every 2 weeks from 8 to 36 weeks' gestation and weekly until delivery (6). This means 15 scheduled face-to-face visits, requiring women to take a morning, afternoon, or full day off work and/or arrange childcare provision. In addition, there are frequent between-visit contacts (face-to-face, telephone, and e-mail) with the diabetes educator for glycemic management. The increased use of technology has the potential to deliver antenatal diabetes care more efficiently to a larger number of women and more effectively in terms of optimizing day-to-day glucose control. In light of increasing demands on limited health care resources, cost-effective diabetes technologies, which enable women to effectively self-manage before, during, and between their pregnancies, are urgently needed. This article will review the progress in our understanding of the intensive glycemic treatment of T1D pregnancy, focusing in particular on the recent technological advances in continuous glucose monitoring (CGM) and automated insulin delivery.

PREPREGNANCY CARE

While hyperglycemia at any stage of pregnancy is associated with increased risk of neonatal complications, early pregnancy (the first 6–7 weeks), when organogenesis of major cardiac and neural tube structures occurs, is particularly crucial (7). Hyperglycemia, lack of folic acid supplementation, and taking potentially harmful medications (ACE inhibitors, statins) all contribute to increased rates of cardiac and neural tube anomalies. Tennant et al. (8) demonstrated that even in normally formed offspring without congenital anomaly, the increased risk of fetal and infant death is still largely moderated by maternal glycemic control. Periconception HbA_{1c} levels >6.3% (43 mmol/mol) are associated with increased odds of congenital anomaly, and levels >6.6% (49 mmol/mol) are associated with fetal and neonatal death (8). Therefore, prepregnancy care is universally recommended to optimize maternal glycemia and reduce the most serious adverse pregnancy outcomes.

For women with T1D, the key components of prepregnancy care include preconception folic acid supplementation, the lowest HbA_{1c} level that is safely achievable, and stopping potentially harmful medications (6). Our own work has shown that even with intensive antenatal support, women who do not attend prepregnancy care clinics do not achieve the same glycemic control as those who began before pregnancy (9). A concern is that prepregnancy care clinics benefit educated, advantaged women and fail to engage disadvantaged women who should be prioritized to ensure fairness. This is supported by the U.K. National Pregnancy in Diabetes (NPID) audit data, which show that among women living in the most advantaged areas, 75% take 5 mg preconception folic acid and 25% achieve the National Institute for Health and Care Excellence–recommended HbA_{1c} target of <6.5% (48 mmol/mol) (3). Less than 10% of women from disadvantaged areas achieve the same glycemic target. More innovative community-based approaches engaging primary care physicians and using mobile health technology to raise women's awareness of and engagement with prepregnancy care should be targeted at disadvantaged groups. Evaluation of a Danish app designed for women attending a diabetes pregnancy clinic reported that 75% of women had downloaded it, with almost half having engaged with it, prior to pregnancy (10).

ASSESSING GLUCOSE CONTROL IN PREGNANCY—WHAT'S THE BEST TEST?

It is widely accepted that HbA_{1c} levels can be misleading when evaluating individual rather than population-level glucose control, as individuals with the same mean glucose can have different HbA_{1c} values (11). Furthermore, HbA_{1c} does not reflect intra- and interday glycemic excursions or quantify the postprandial hyperglycemia that contributes to fetal and neonatal complications. In women without diabetes, HbA_{1c} is lower during pregnancy due to lower mean glucose, increased erythropoiesis, and shortened red cell life span (12). Extant literature suggests an artifactual lowering of HbA_{1c} (~0.5%) in pregnancy that is unrelated to maternal glycemia (13,14). However, despite its well-recognized gestational limitations (13,14), HbA_{1c} is routinely used to assess maternal glycemia, potentially providing false reassurance to women and clinicians.

Data from our own clinic population of 102 T1D pregnant women found that the relationship between mean self-monitored blood glucose (SMBG) and HbA_{1c} changed in early pregnancy. We found an even larger fall in HbA_{1c}, of ~1% (11 mmol/mol), between 12 and 20 weeks' gestation that was also unrelated to maternal glucose control (Table 1). This means that a mean SMBG of 144 mg/dL (8.0 mmol/L) was associated with an HbA_{1c} of 6.8% (51 mmol/mol) at 12 weeks and with an HbA_{1c} level of 5.9% (41 mmol/mol) at 24 weeks, supporting the view that maternal HbA_{1c} does not adequately reflect antenatal glycemic control (15).

HbA_{1c} can be now calculated according to estimated average glucose (eAG) from CGM measures rather than measured by laboratory assay. Law et al. (16) found that during pregnancy, a 1% (11 mmol/mol) difference in maternal HbA_{1c} is equivalent to 12 mg/dL (0.66 mmol/L) in average glucose levels. Thus, HbA_{1c} is also associated with lower eAG in pregnancy, leading to a recommendation that pregnancy-specific calculations be used and reported. This difference between the pregnancy-specific and nonpregnancy eAG increases with increasing HbA_{1c} values, which means that HbA_{1c} values can be particularly misleading and falsely reassuring in those with suboptimal glycemic control. These authors suggest that patients and clinicians should aim for eAG of 6.4–

Table 1—Changes in mean glucose, HbA_{1c}, and percentage of capillary glucose levels >8 mmol/L (144 mg/dL) during T1D pregnancy

Gestation	Mean glucose, mmol/L	HbA_{1c}, %	HbA_{1c}, mmol/mol	% Glucose >8 mmol/L (144 mg/dL)
Booking‡		7.6 ± 1.4	60 ± 15	
12 weeks	7.8 ± 1.5	6.8 ± 1.0	51 ± 11	39.9 ± 15.7
16 weeks	7.4 ± 1.2	6.3 ± 0.9	45 ± 10	35.2 ± 13.0
20 weeks	7.3 ± 1.1	5.9 ± 0.8	41 ± 9	35.1 ± 13.0
24 weeks	7.4 ± 1.0	5.8 ± 0.8	40 ± 9	35.2 ± 13.8
28 weeks	7.3 ± 1.1	5.9 ± 0.8	41 ± 9	35.4 ± 13.3
32 weeks	7.1 ± 1.0	5.9 ± 0.7	41 ± 8	33.8 ± 12.3

Data are mean ± SD. ‡These data are provided courtesy of Dr. Rosemary Temple and Dr. Katharine Stanley from the Norfolk and Norwich University Hospital NHS Foundation Trust antenatal diabetes clinic. The mean gestational age at the first (booking) visit was 7.2 ± 2.2 weeks, with 80 (78%) women seen at ≤8 weeks and 90 (88%) at ≤10 weeks.

6.7 mmol/L to minimize risk of LGA (16). This practical solution is applicable to SMBG users (with memory glucometers to calculate a mean glucose over 7–14 days) as well as insulin pump and CGM users.

Novel Markers of Glycemic Control

1,5-Anhydroglucitiol has been approved by the U.S. Food and Drug Administration (FDA) for intermediate assessment of glycemic control and may have a role during pregnancy, reflecting postprandial glycemic excursions (17). More recently, the complement inhibitor glycated CD59 has been suggested as a novel marker of glycemic control (18). It may be useful for identifying pregnancies complicated by hyperglycemia and for identifying mothers at increased risk of delivering LGA newborns. Approximately 75% of LGA infants were born to mothers with a sevenfold increase in median CD59 levels but apparently "normal" results during an oral glucose tolerance test (18). Whether or not these novel markers will prove useful in clinical practice is unclear, especially as direct CGM measures become increasingly used.

CGM Metrics

The vast array of direct CGM metrics facilitates more detailed objective measurement of day-to-day glucose control but complicates our definition of "good" glycemic control. HbA_{1c} lends itself to clear thresholds, with almost all professional organizations suggesting targets of <6.5% (48 mmol/mol) during pregnancy. Similar targets for CGM measures have not yet been established. Outside of pregnancy, there is a move toward standardization of definitions for time spent in the target glucose range (time in range [TiR]) and for both hypo- and hyperglycemic excursions (19). This allows for between-study comparisons and is particularly relevant for T1D pregnancy where CGM data are limited. Suggested CGM metrics for pregnancy in relation to the recent international consensus statement (19) are proposed in Table 2.

CGM accuracy is most commonly assessed using the mean absolute relative difference (MARD) between CGM and SMBG values. A MARD ≤10% is optimal for research and for clinical decision making and is applicable regardless of pregnancy status. The percentage TiR target range is usually 70–140 mg/dL or 63–140 mg/dL during T1D pregnancy, lower than the 70–180 mg/dL (3.9–10.0 mmol/L) range outside pregnancy. The consensus statement suggests categorizing the level of hypoglycemia into levels of increasing severity from level 1 to level 3. Level 1 is an alert of potential impending hypoglycemia. Level 2 is a glucose level <54 mg/dL (3.0 mmol/L) with or without symptoms. Level 3 is a severe hypoglycemia episode requiring assistance. As fasting glucose is lower during pregnancy and sensor accuracy is lower in the hypoglycemic range, paying attention to the lower threshold is important when quantifying hypoglycemia. Diabetes pregnancy clinicians need to consider whether to adapt the standardized international thresholds or to establish pregnancy-specific ones using the more stringent T1D pregnancy thresholds of 63 mg/dL (3.5 mmol/L) and 50 mg/dL (2.8 mmol/L).

GLYCEMIC CONTROL IN PREGNANT WOMEN

It has been a decade since we first described the longitudinal CGM measures during T1D pregnancy. These data provided some of the first insights into direct fetal exposure to maternal hyperglycemia (20). Our original CGM data indicated that T1D women spent only 43% TiR of 70–140 mg/dL (10.4 h/day) in early pregnancy, rising to 56% (13.5 h/day) in late pregnancy (20). Despite enormous efforts, they still spent 33% of the time (8 h/day) hyperglycemic (>140 mg/dL) during the third trimester. Maternal hypoglycemia (<70 mg/dL) was widespread, ~13% (3 h/day). Very comparable findings were reported in women with T1D from a Danish CGM trial using SMBG measures: 58% in target (70–144 mg/dL), 14% below 70 mg/dL, and 28% above the slightly higher 144 mg/dL hyperglycemic threshold (21).

Comparing these data with the recent Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) data, the third trimester TiR (63–140 mg/dL) is largely unchanged: 61% in the SMBG group (22) (Fig. 1*A*). The most striking difference is the substantial reduction in maternal hypoglycemia (Fig. 1*B*). The CONCEPTT CGM group spent only 3% time below 63 mg/dL compared with 13–14% time below 70 mg/dL in the earlier CGM studies. This is not only due to differences in sensor accuracy or hypoglycemia thresholds, as clinical hypoglycemia events and severe hypoglycemia episodes were also reduced, most likely due to increasing use of insulin analogs (23,24).

However, the fetal exposure to maternal hyperglycemia is essentially unchanged in routine care. Women using CGM spent 5% (1.2 h/day) less time hyperglycemic (27 vs. 32%) at 34 weeks' gestation (Fig. 1*C*) (22). However, pregnant women using only SMBG still spent 45% time (11.5 h/day) hyperglycemic at 24 weeks' gestation, which likely explains why LGA rates remain persistently high (25).

CGM allows for unprecedented characterization of the day-to-day, within-day,

Table 2—Consensus statement recommendations with suggestions for T1D pregnancy

	Nonpregnant	Pregnant
Data sufficiency	70–80% of possible CGM data	70–80% of possible CGM data
Data duration	Minimum of 2 weeks	Not determined
Time blocks	24 h (midnight to midnight)	24 h (midnight to midnight)
Nighttime	2400–0600 h	2400–0600 or 2300–0700 h
Daytime	0600–2400 h	0600–2400 or 0700–2300 h
Overall control	Mean glucose	Mean glucose
% TiR	70–180 mg/dL (3.9–10.0 mmol/L) 70–140 mg/dL (3.9–7.8 mmol/L)	70–140 mg/dL (3.9–7.8 mmol/L) 63–140 mg/dL (3.5–7.8 mmol/L)
Hyperglycemia, level 1	>180 mg/dL (10.0 mmol/L)	>140 mg/dL (7.8 mmol/L)
Hyperglycemia, level 2	>250 mg/dL (13.9 mmol/L)	>180 mg/dL (10.0 mmol/L)
High glucose exposure	High blood glucose index	High blood glucose index
Hypoglycemia, level 1	<70–54 mg/dL (3.9–3.0 mmol/L)	<70–54 mg/dL (3.9–3.0 mmol/L) or 63–50 mg/dL (3.5–2.8 mmol/L)
Hypoglycemia, level 2	<54 mg/dL (3.0 mmol/L)	<54 mg/dL (3.0 mmol/L) or <50 mg/dL (2.8 mmol/L)
Hypoglycemia, level 3	Severe hypoglycemia	Severe hypoglycemia
Low glucose exposure	Low blood glucose index	Low blood glucose index
Hypoglycemic event	15-min duration	15-min duration
Prolonged hypoglycemia	120 min	120 min
Glycemic variability		
SD	Not reported	<25 mg/dL suggested
Coefficient of variation	<36% (stable glycemia)	<36% (stable glycemia)
For research purposes		
AUC	AUC level 1 and 2 hyperglycemia	AUC level 1 and 2 hyperglycemia
	AUC level 1 and 2 hypoglycemia	AUC level 1 and 2 hypoglycemia
Composite glycemic trial outcomes	HbA_{1c} or TiR and level 2 hypoglycemia	TiR and level 2 hypoglycemia
Broader composite outcomes	HbA_{1c} or TiR + hypoglycemia + lipids + BP + weight gain	TiR + hypoglycemia + gestational weight gain + obstetric/neonatal outcomes

Optimal sensor accuracy is considered as MARD ≤10% in pregnant and nonpregnant settings. AUC, area under the curve.

and between-day glycemic variability, with a vast array of potential metrics assessing the amplitude, frequency, and duration of deviations above and below target range. Most of these measures are highly correlated and dependent on mean glucose, making it difficult to accurately assess the independent contribution of glycemic variability beyond overall glucose control. Importantly, the risk of maternal and/or fetal complications increases both with amplitude and with duration of the glycemic excursion, yet most of the traditional glycemic variability metrics ignore the time axis of CGM data. More sophisticated statistical methods (time series, functional data analysis) may provide new insights into which time periods (day vs. night) to target glycemic interventions (26).

GLYCEMIC CONTROL IN WOMEN PLANNING PREGNANCY

Even with specialist prepregnancy care clinics and motivated advantaged attendees, only a third to a half of attendees achieve target HbA_{1c} levels before conception (9,27). The recent CONCEPTT specifically evaluated the effectiveness of CGM for improving glucose control in women planning pregnancy. Previous studies have evaluated the role of retrospective and/or intermittent real-time CGM during pregnancy (21,28) but did not include women planning pregnancy. Full details of the study protocol and results are published elsewhere (22,29). In brief, there were 53 women assigned to CGM and 57 to SMBG (control). They had a long duration of diabetes (18 and 19 years, respectively), with correspondingly high rates of microvascular complications (37%). There was widespread use (~75%) of insulin pump therapy. Importantly, most women were already overweight or obese, with only 40% having a preconception BMI of ≤25 kg/m^2.

The frequency of CGM use (Guardian or MiniMed MiniLink system) was reasonably high over the first 3 months (median 6.7 days), with some attenuation over 6 months (median 6.2 days). HbA_{1c} fell in both groups (7.6% [59 mmol/mol] to 7.1% [54 mmol/mol] and 7.3% [56 mmol/mol] in the CGM and SMBG groups, respectively), with 50% of CGM and 40% of SMBG women reaching target HbA_{1c} levels. However, as both groups improved, the between-group differences were small and not statistically significant. Likewise, although the direct CGM measures favored CGM, with greater reductions in mean glucose (from 158 to 144 mg/dL [8.8 to 8.0 mmol/L]) and more of an increase in TiR of 63–140 mg/dL (from 42 to 48%), these were not statistically significant. Thirty-four women conceived (17 CGM, 17 control), and their glucose control (mean HbA_{1c} at confirmed pregnancy 6.9 vs. 7.0% [52 vs. 53 mmol/mol]) and pregnancy outcomes did not differ. Although the numbers of women who conceived were very small, there was 3-kg less gestational weight gain in the CGM group (10.4 vs. 13.4 kg from confirmed pregnancy to 34 weeks' gestation), suggesting that CGM users may have been making substantial dietary adjustments.

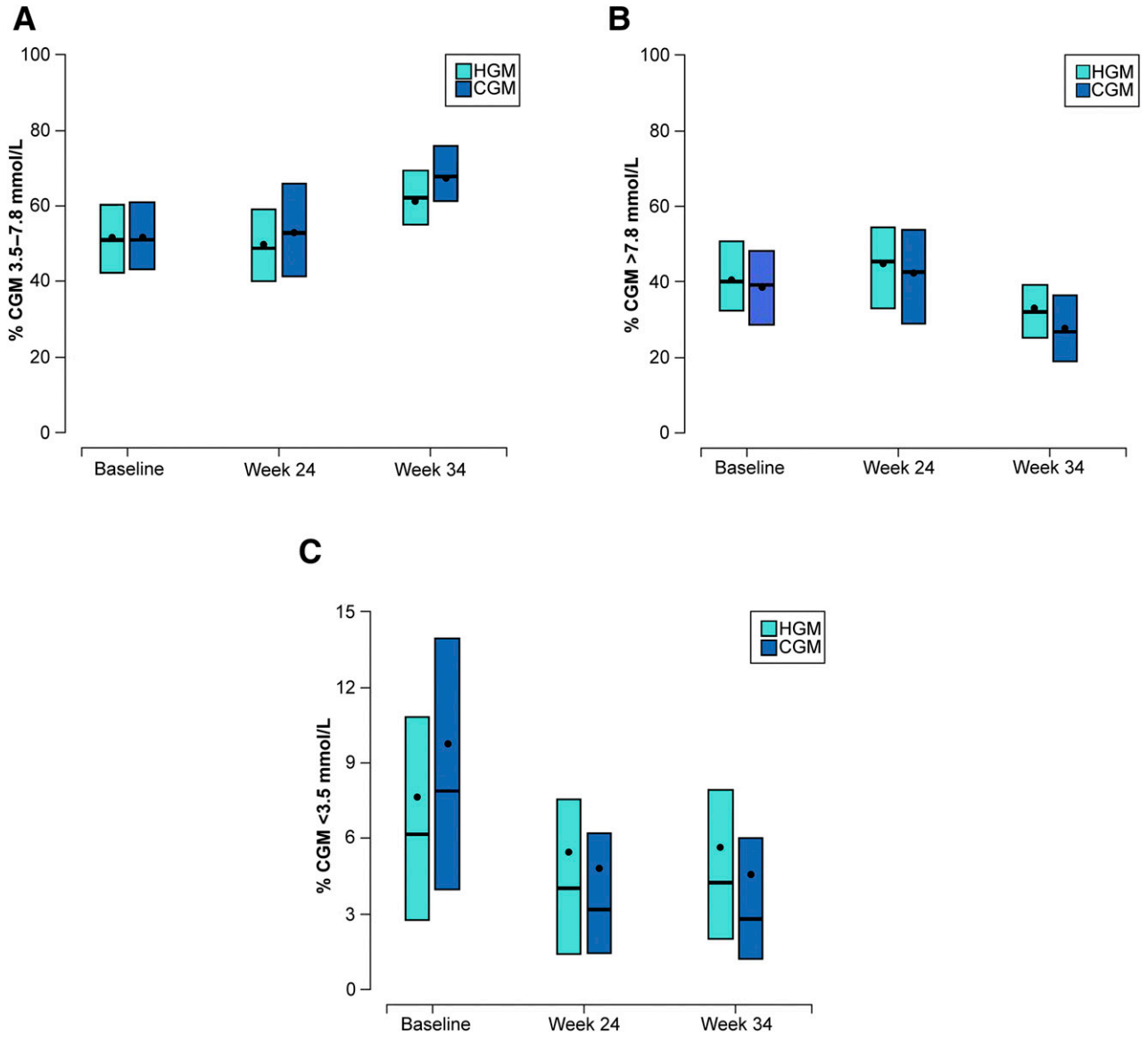

Figure 1—CGM measures of women with T1D during pregnancy in CONCEPTT. *A*: Time in T1D pregnancy target range 63–140 mg/dL (3.5–7.8 mmol/L). The home glucose monitoring (HGM) control group spent 52% TiR at baseline (12.5 h/day), rising to 61% (14.6 h/day) at 34 weeks' gestation. The CGM group spent 52% TiR at baseline (12.5 h/day), rising to 68% (16.3 h/day) at 34 weeks' gestation. *B*: Time spent hyperglycemic (>140 mg/dL [7.8 mmol/L]). The HGM control group spent 40% time hyperglycemic at baseline (9.6 h/day), reducing to 32% (7.7 h/day) at 34 weeks' gestation. The CGM group spent 39% time hyperglycemic at baseline (9.4 h/day), reducing to 27% (6.5 h/day) at 34 weeks' gestation; $P = 0.03$. *C*: Time spent hypoglycemic (<63 mg/dL [3.5 mmol/L]). The HGM control group spent 8% time hypoglycemic at baseline (1.9 h/day), reducing to 4% (1.0 h/day) at 34 weeks' gestation. The CGM group spent 6% time hypoglycemic at baseline (1.4 h/day), reducing to 3% (0.7 h/day) at 34 weeks' gestation; $P = 0.10$. This figure is reproduced with permission from Yamamoto and Murphy (48).

Despite adjustments to diet and glycemia, 75% of these babies had a composite poor outcome, which included miscarriage, LGA, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress, and NICU admission. These data do not mean that CGM and/or sensor-augmented pump therapy are ineffective, but they highlight that despite increased use of advanced diabetes technology, euglycemia in T1D pregnancy remains elusive before and during pregnancy.

INSULIN DELIVERY: PENS VERSUS PUMPS

An unexpected finding from CONCEPTT was that the treatment effect of CGM was comparable in women using insulin pumps and multiple daily injections (MDI). This supports recent data supporting CGM use in MDI users outside of pregnancy (30). Indeed, in CONCEPTT, the CGM MDI users had the best overall glucose control, with almost 70% TiR (63–140 mg/dL), 26% time >140 mg/dL, and 3% time <63 mg/dL (Table 3). Furthermore, their glycemic variability was comparable to that of insulin pump users. Some authors have suggested that insulin pump therapy has not yet lived up to the expectations of health care professionals (31). The randomized studies in pregnancy are outdated, with older pumps and MDI regimes and small sample sizes, and are not applicable to current clinical practice (32). More recent descriptions are observational and subject to bias and confounding factors

Table 3—CGM measures among women in CONCEPTT using insulin pump and MDI during pregnancy

	Pump users (*N* = 98)			
	10–11 weeks' gestation		34–35 weeks' gestation	
	CGM (*N* = 50)	Control (*N* = 48)	CGM (*N* = 35)	Control (*N* = 37)
Mean glucose, mg/dL	131 ± 22	133 ± 22	121 ± 18	126 ± 16
% TiR*	53 ± 12	54 ± 14	66 ± 13	62 ± 14
% Time >140 mg/dL	39 (26–47)	39 (29–49)	27 (20–37)	32 (27–41)
% Time <63 mg/dL	8 (3–13)	6 (3–10)	3 (1–7)	4 (2–7)
Hypoglycemia episodes**	0.8 (0.6–1.0)	0.7 (0.5–0.9)	0.5 (0.3–0.8)	0.5 (0.4–0.7)
Coefficient of variation, %	42 (37–47)	40 (36–46)	31 (28–37)	35 (29–40)
SD, mmol/L	3.0 (2.5–3.4)	3.1 (2.5–3.6)	2.2 (1.8–2.5)	2.4 (2.0–3.0)
	MDI users (*N* = 116)			
	10–11 weeks' gestation		34–35 weeks' gestation	
	CGM (*N* = 57)	Control (*N* = 59)	CGM (*N* = 42)	Control (*N* = 40)
Mean glucose, mg/dL	131 ± 22	139 ± 18	121 ± 14	126 ± 7.0
% TiR*	50 ± 13	50 ± 13	69 ± 13	61 ± 17
% Time >140 mg/dL	39 (30–49)	41 (34–51)	26 (17–36)	31 (24–39)
% Time <63 mg/dL	8 (5–17)	6 (2–12)	3 (1–6)	5 (2–9)
Hypoglycemia episodes**	0.8 (0.6–1.0)	0.7 (0.3–0.9)	0.5 (0.3–0.8)	0.5 (0.3–0.8)
Coefficient of variation, %	43 (39–48)	43 (36–49)	33 (28–37)	34 (29–38)
SD, mmol/L	3.2 (2.7–3.6)	3.2 (2.7–3.9)	2.2 (1.8–2.5)	2.3 (2.0–2.8)

Data are mean ± SD and median (interquartile range) as appropriate. These data are adapted from the CONCEPTT results publication (22). *TiR for T1D pregnancy was defined as 63–140 mg/dL (3.5–7.8 mmol/L). **Hypoglycemia episodes were defined as CGM levels <63 mg/dL for at least 20 min. Distinct episodes were counted only if separated by at least 30 min.

(31,33). Pumps are now in such widespread clinical use among women of reproductive years that an adequately powered, randomized trial would not be feasible in most antenatal diabetes clinics, with appropriate diabetes technology infrastructure and educator expertise.

A pragmatic randomized controlled trial evaluating the relative effectiveness of pumps over MDI in nonpregnant U.K. participants found a mean change in HbA_{1c} at 24 months of −0.8% and −0.4% (−9 and −4.5 mmol/mol) for pump and MDI users, respectively (34). After adjustment for confounders, the difference in favor of pump users was smaller (−0.24% [−2.7 mmol/mol]) and not statistically significant. The accompanying psychosocial evaluation found that pump users showed greater improvement in diabetes treatment satisfaction, more dietary freedom, and fewer diabetes hassles (35). This supports an emerging point of view that pump therapy may be more beneficial for psychosocial outcomes than for glycemic outcomes. CGM, with all its alarms and annoyances, may be more effective for focusing the mind on minimizing glycemic excursions.

RECENT DEVELOPMENTS IN CGM ACCESSIBILITY

While there have been incremental improvements in sensor accuracy and usability over the past decade, there have been three key developments in terms of CGM accessibility. These include a growing evidence base regarding the clinical effectiveness in MDI users (30), the FDA approval of CGM measures for insulin dosing, and the introduction of the FreeStyle Libre, the first factory-calibrated intermittent glucose monitoring system (30,36). Data from the T1D Exchange registry showed very little CGM use (<10%) compared with widespread insulin pump use (60%) during 2013–2014 (37). However, the increasing recognition that CGM benefits both pump and MDI users means that CGM is becoming more applicable for day-to-day glycemic management for a wider patient population (22,30).

The FDA endorsement of real-time CGM (specifically the Dexcom G5) for replacing SMBG is also an important step forward. While calibration and some checking of SMBG is still recommended, particularly during hypoglycemia, exercise, and driving, both the clinical and cost-effectiveness of CGM will be greatly enhanced with sensors accurate enough for premeal insulin dosing. The longer duration of newer generation sensors, lasting for up to 10 days, will benefit users and payers and further improve CGM accessibility.

The real game-changer is the introduction of the FreeStyle Libre (Abbott Diabetes Care) intermittent glucose monitoring system (36). The sensors last 14 days without the need for additional SMBG calibration tests. It is so easy and intuitive that it is marketed directly to consumers (without the need for physician recommendation) and neither patient nor staff training is required. When it was first introduced in the U.K., there was such overwhelming demand that the early supply was inadequate, requiring new manufacturing premises to be built. It is also the first CGM to obtain a specific label for use during pregnancy. A study among 74 pregnant women (39 with gestational diabetes mellitus, 24 with T1D, and 11 with T2D) across 13 sites (9 U.K. and 4 Austrian) demonstrated that, as expected, sensor accuracy, assessed over 14 days at various gestational ages, is comparable (MARD of ~12%) in pregnant and nonpregnant users (38). We found similar agreement between CGM sensor accuracy for pregnant and nonpregnant users of the Navigator sensor when compared with plasma glucose (39). While other sensors may not have specific licenses for use in pregnancy, it seems that accuracy issues are sensor specific and applicable to pregnant and nonpregnant users. The professional version of the FreeStyle Libre (available in the U.S.) will improve the documentation of glycemic profiles in pregnancy. It provides 14-day masked glucose profiles without requiring SMBG, making it an accessible and affordable research tool.

The obvious appeal of the FreeStyle Libre in clinical practice is the lack of alarms and burdens that are associated with real-time CGM. Data from the T1D Exchange indicate that use of real-time CGM wanes over time and that optimal use as seen in the setting of randomized controlled trials is not widespread (37). If real-time CGM is a high-cost, high-maintenance diabetes companion, the FreeStyle Libre is its low-cost, low-maintenance alternative. Although it still provides real-time continuous glucose data on demand (by scanning the reader), it does not alarm to alert users

of out-of-range or rapidly changing glucose levels.

Real-world data provided by the device manufacturers suggest that the benefits on glucose control increase with more frequent glucose checking (36). The estimated HbA_{1c} reductions were most marked (from 8 to 6.7% [64 to 50 mmol/mol]) in users with the most frequent glucose checks (increasing from 4 to 48 checks per day). The average user performed 16.3 checks daily, which is clearly higher than an average SMBG user. The role of FreeStyle Libre in T1D pregnancy is yet to be determined, as is, in particular, whether it is as effective as real-time CGM for improving neonatal outcomes (22). The FreeStyle Libre may be an excellent "entry level" technology for patients not wanting the demands of real-time CGM. It may also help clinicians to determine which patients are candidates for more advanced CGM, sensor-augmented/threshold suspend pumps, and automated insulin delivery systems.

AUTOMATED INSULIN DELIVERY

Technological advances in CGM have made the promise of automated insulin delivery, also known as artificial pancreas or closed-loop insulin delivery, a potential clinical therapeutic reality. A recent systematic review and meta-analysis of 585 participants from 27 outpatient studies found consistent glycemic improvements with 12.6% increased TiR (3 h/day) across a variety of closed-loop systems (40). However, thus far, most of the improvement is in overnight glycemia and the between-group differences are very dependent on the level of glucose control in the comparator arm. We also found that overnight closed-loop insulin delivery was associated with a 15% higher overnight time in target range (75 vs. 60%) during T1D pregnancy (41). Preliminary data from this first home closed-loop study suggest feasibility of day-and-night closed-loop therapy throughout pregnancy, including in the hospital during labor and delivery. Most women chose to continue closed-loop therapy after the randomized trial, with generally high levels of satisfaction despite frequent alarms and technical glitches (42).

A subsequent randomized evaluation of day-and-night closed-loop therapy in T1D pregnancy found that closed-loop was as effective as, but not superior to, sensor-augmented pump therapy (43). Women spent 60% TiR during both interventions in the second trimester, but closed-loop therapy reduced the extent and duration of hypoglycemia, suggesting that it is potentially safer. We also found that women who entered pregnancy with better glucose control achieved a fairly constant 70–75% TiR (63–140 mg/dL) across pregnancy. Women with suboptimal glucose control (HbA_{1c} >7.5% [53 mmol/mol]) never caught up and only achieved 65–70% TiR after 28 weeks' gestation. They took longer to become confident using the study devices and never quite reached the same glycemic control, suggesting that diabetes self-management education is still required for optimal use of hybrid closed-loop systems (11). Other investigators have also warned that automated insulin delivery should not be considered a hands-off option and should be accompanied by appropriate high-quality dietary and diabetes education (11). This is particularly important during pregnancy when the tight postprandial glucose targets require meticulous attention to carbohydrate estimation and bolusing at least 15–30 min before eating (44).

As most women with T1D are now entering pregnancy overweight (35%) or obese (25%), the importance of optimal dietary intake cannot be overstated (3,22). Higher prepregnancy BMI and higher gestational weight gain, independent of maternal BMI and glycemic control, is associated with increasing neonatal birth weight (45). We found that almost half of the total daily carbohydrate intake of U.K. participants in CONCEPTT was from ultra-processed, high-sugar (biscuits, chocolate, and confectionary) sources. This means that these well-educated, motivated pregnant women ate ~90 g per day of fast-acting added sugars, with little if any nutritional value. There are no fast-acting insulin analogs currently available (or on the horizon) that will be able to safely match these dietary intakes during pregnancy (46).

A recent systematic review and meta-analysis found 19 randomized controlled trials of dietary interventions in gestational diabetes mellitus pregnancy (47). While dietary advice is an increasingly recognized important component of clinical management in T1D pregnancy, there are no evidence-based data to guide clinical practice. A high-quality dietary intervention trial (perhaps of Mediterranean diet or low glycemic index carbohydrates or interventions to minimize consumption of ultra-processed foods) is required to guide optimal implementation of CGM, continuous subcutaneous insulin infusion, and closed-loop delivery in T1D pregnancy. While advanced diabetes technology may add an additional 5–10% time in target range (and possibly more for those with suboptimal glucose control) in T1D pregnancy, optimizing maternal dietary intake is imperative to minimize the immediate and longer-term consequences of postprandial hyperglycemia.

Acknowledgments. I acknowledge the invaluable support from the multidisciplinary diabetes teams at Cambridge University Hospitals NHS Foundation Trust, Cambridge, U.K. (Caroline Byrne, Katy Davenport, Jeannie Grisoni, Kerry Stubbington, Ruth Harding, and Charlotte Patient), Ipswich Hospital NHS Trust, Ipswich, U.K. (Sue Mitchell, Anne Scott, Damian Morris, and Duncan Fowler), and Norfolk and Norwich University Hospital, Norwich, U.K. (Rosemary Temple, Katherine Duffield, Katharine Stanley, and Mike Sampson). I also thank Gerry Rayman (Ipswich Hospital NHS Trust, Ipswich, U.K.) and the Ipswich diabetes team for teaching me (from scratch) the principles of diabetes self-management education and Timothy Skinner (Charles Darwin University, Australia) for encouragement to always "ask a better question." I thank Dr. Rosemary Temple for kitchen table discussions that have guided my entire diabetes pregnancy research. Likewise, I am indebted to Elisabeth Mathiesen (Rigshospitalet, Copenhagen, Denmark) for her mentorship, friendship, support, and support for truly collaborative research. I thank the entire CONCEPTT team, in particular Denice Feig (University of Toronto, Canada) for an effective, fun, and productive partnership. Finally, I thank the inspiring efforts of Dr. Roman Hovorka (University of Cambridge, Cambridge, U.K.) and the University of Cambridge artificial pancreas team (in particular Janet Allen, Daniella Elleri, Gosia Wilinska, Kavita Kumareswaran, Leelarathna Lalantha, Hood Thabit, Sara Hartnell, and Zoe Stewart) and Dr. Eleanor Scott (University of Leeds, Leeds, U.K.) for making automated insulin delivery a potential therapeutic option in T1D pregnancy.

Funding. H.R.M. conducts independent research supported by the National Institute for Health Research (NIHR) (CDF-2013-06-035). She has also received grant income from the U.K. Efficacy Mechanism Evaluation programme (funded by the Medical Research Council and NIHR), Diabetes UK, JDRF, and Diabetes Research & Wellness Foundation.

The views expressed in this publication are those of the author and not necessarily those of the National Health Service, NIHR, or the U.K. Department of Health.

Duality of Interest. H.R.M. serves on the Medtronic European Scientific Advisory Board.

Prior Presentation. Parts of this article were presented at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 23 June 2018.

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