Title: Intensive Glycemic Treatment during Type 1 Diabetes Pregnancy: A story of (mostly) sweet success!

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Word count: Abstract 246, main text 3927

Tables: 3

Figures: 1

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Unstructured Abstract:

Studies from Scotland and Canada confirm large increases in the incidence of pregnancies complicated by pre-gestational 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), in stillbirths (UK) and substantial reductions in maternal hypoglycemia (both moderate and severe) across many countries. However, pregnant women with T1D still spend approximately 30-45% of the time (8-11 hours/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 explains the persistently rates of large for gestational age (LGA), neonatal hypoglycemia and neonatal intensive care unit (NICU) admissions in T1D offspring. The CONCEPTT trial found that pregnant women using real-time Continuous Glucose Monitoring (CGM) spent 5% less time (1.2 hours/day) hyperglycemic during the third trimester, with clinically relevant reductions in LGA, neonatal hypoglycemia and NICU admissions. This perspective 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 minimise the neonatal complications attributed to maternal hyperglycemia.

Introduction

Prospective nationwide studies confirm that despite widespread suboptimal glycemic control, the majority of women with pre-gestational type 1 diabetes deliver live born babies (1, 2). Whilst 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 liveborn infant. A large population-based study from the United Kingdom reported a consistent reduction in stillbirths, from 25.8 to 10.7 per thousand births, in women with pre-gestational diabetes over the past decade (3). The absolute risk of stillbirth in T1D is now between 10–13 per thousand births, which although higher than the background maternity population risk of <5 per thousand, 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 for women with diabetes (5). Both the Canadian and Scottish studies describe significant increases in the incidence of pregnancies complicated by pre-gestational diabetes over the past 15 years (a doubling in Canada and a 44% increase in T1D and 90% T2D in Scotland) (4, 5).

The reasons for reductions in stillbirths are most likely multifactorial including for example; improvements in the provision and uptake of prepregnancy care, tighter glycemic targets (HbA1c <6.5% (48 mmol/mol) and increased specialization of antenatal diabetes care. Since 2002-03, the number of UK diabetes maternity clinics has reduced (from 231 to 155), while the incidence of pregnancies complicated by pre-gestational diabetes has increased. This means that there are now twice as many women with pre-gestational 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, diabetes dietitian) typically every 2 weeks from 8-36 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 email) 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 optimising day-to-day glucose control. In a background of increasing demands on limited health care resources cost-effective technologies, which enable women to effectively self-manage before, during and between their pregnancies, are urgently needed. This perspective 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.

Prepregnancy care

While hyperglycemia at any stage of pregnancy is associated with increased risk of neonatal complications, early pregnancy (the first six to seven weeks), when organogenesis of major cardiac and neural tube structures occur 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 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 (8). Periconception HbA1c levels above 6.3% (43mmol/mol) are associated with increased

odds of congenital anomaly and levels above 6.6% (49mmol/mol) with fetal and infant death (8). Therefore, prepregnancy care (PPC) is universally recommended, to optimise maternal glycemia and reduce the most serious adverse pregnancy outcomes.

For women with T1D, the key components of PPC include preconception folic acid supplementation, the lowest HbA1c 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 PPC clinics do not achieve the same glycemic control as those who began before pregnancy (9). A concern is that PPC clinics benefit educated, advantaged women and fail to engage disadvantaged who should be prioritised to ensure fairness. This is supported by the UK National Pregnancy In Diabetes (NPID) audit data which shows that among women living in the most advantaged areas, 75% take 5mg preconception folic acid and 25% achieve the NICE recommended HbA1c target of <6.5% (48mmol/mol)(3). Fewer than 10% of women from disadvantaged areas achieve the same HbA1c target. More innovative approaches such as Mobile health (mHealth) technology to raise womens awareness of and engagement with PPC 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 engaging with it, prior to pregnancy (10).

Assessing glucose control in pregnancy – what's the best test?

It is widely accepted that HbA1c levels can be misleading when evaluating individual rather than population level glucose control as individuals with the same mean glucose can have different HbA1c values (11). Furthermore, HbA1c does not reflect intra- and interday glycemic excursions or quantify the postprandial hyperglycemia that contributes to fetal and neonatal complications. In women without diabetes, HbA1c is lower during pregnancy, due

to lower mean glucose, increased erythropoiesis and shortened red cell life span (12). Extant literature suggests an artefactual lowering of HbA1c (approximately 0.5%) in pregnancy that is unrelated to maternal glycemia (13, 14). However, despite its well-recognized gestational limitations (13, 14), HbA1c 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 HbA1c changed in early pregnancy. We found an even larger fall in HbA1c, of approximately 1% (11mol/mol), between 12 and 20 weeks gestation that was also unrelated maternal glucose control (Table 1). This means that a mean SMBG of 144mg/dl (8.0 mmol/L) was associated with an HbA1c of 6.8% (51mmol/mol) at 12 weeks and with an HbA1c level of 5.9% (41mmol/mol) at 24 weeks gestation, supporting the view that maternal HbA1c does not adequately reflect antenatal glycemic control (15).

HbA1c can be now calculated according to estimated average glucose (eAG) from CGM measures rather than measured by laboratory assay. Law et al found that during pregnancy, a 1% (11mmolmol) difference in maternal HbA1c is equivalent to 12mg/dl (0.66 mmol/L) in average glucose levels (16). Thus, HbA1c 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 non-pregnancy eAG increase with increasing HbA1c values, which means that HbA1c 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 6.4-6.7mmol/L to minimise 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 (1,5-AG) has been approved by the Food and Drug Administration (FDA) for intermediate assessment of glycaemic control and may have a role during pregnancy, reflecting post-prandial 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 7-fold increase in median CD59 levels but apparently "normal" results during an oral glucose tolerance test (18). Whether or not these will prove useful in clinical practice is unclear, especially as direct CGM measures become increasingly available.

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. HbA1c lends itself to clear thresholds with almost all professional organizations suggesting targets of <6.5% (48mmol/mol) during pregnancy. Similar targets for CGM measures have not yet been established. Outside of pregnancy there is a move towards standardization of definitions for time-in-range (TiR), and 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 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

is usually 70-140mg/dl or 63-140mg/dl during T1D pregnancy, lower than the 70-180mg/dl (3.9-10.0mol/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 <54mg/dl (3.0mmol/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 in pregnancy. Diabetes pregnancy clinicans need to consider whether to adapt the standardized threholds or to establish pregnancy specific ones using the more stringent T1D pregnancy thresholds of 63mg/dl (3.5mmol/L) and 50mg/dl (2.8mmol/L).

Glycemic control in pregnant women

It is 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 70-140mg/dl (10.4 hours/day) in early pregnancy rising to 56% (13.5 hours/day) in late pregnancy (20). Despite enormous efforts, they still spent 33% of the time (8 hours/day) hyperglycaemic >140mg/dl during the third trimester. Maternal hypoglycemia (<70mg/dl) was widespread, approximately 13% (3 hours/day). Very comparable findings were reported in women with T1D from a Danish CGM trial using SMBG measures; 58% in target (70-144mg/dl), 14% below 70mg/dl, and 28% above the slightly higher 144mg/dl hyperglycemic threshold (21) .

Comparing these with the recent CONCEPTT data, the third trimester TiR (63-140mg/dl) is largely unchanged; 61% in the SMBG group (22) (Figure 1a). The most striking difference is the substantial reduction in maternal hypoglycemia (Figure 1b). The CONCEPTT CGM

group spent only 3% time below 63mg/dl compared to 13%-14% time below 70mg/dl in the earlier CGM studies. This is not just due to differences in sensor accuracy or hypoglycemia thresholds as clinical hypoglycaemia events and severe hypoglycaemia episodes were also reduced, most likely due to increasing use of insulin analogues (23, 24).

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

CGM allows for unprecedented characterisation of the day-to-day, within-day 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 increase 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

However, even with specialist PPC clinics and motivated advantaged attendees, only a third to a half of attendees achieve target HbA1c levels before conception (9, 27). The recent CONCEPTT trial specifically evaluated the effectiveness of CGM for improving glucose control in women planning pregnancy. Previous studies had evaluated the role of

retrospective and/of 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 long duration of diabetes (18 and 19 years respectively), with most (approximately 75%) using insulin pump therapy. Their rates of microvascular complications were high (37%). Importantly, most women were already overweight or obese, with only 40% having a preconception body mass index (BMI) of $\leq$25 kg/m^2.

The frequency of CGM use (Guardian or MiniMed Minilink system) was reasonably high over the first three months (median 6.7 days) with some attenuation over six months (median 6.2 days). HbA1c fell in both groups (7.6% (59mmol/mol) to 7.1% (54mmol/mol) and 7.3% (56mmol/mol) in the CGM and SMBG groups respectively) with 50% of CGM and 40% of SMBG women reaching target HbA1c 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 144mg/dl or 8.8 to 8.0mmol/L) and more of an increased TiR of 63-140mg/dl (from 42 to 48%), these were not statistically significant. Thirty four women conceived (17 CGM, 17 control) and their glucose control (mean HbA1c at confirmed pregnancy 6.9% vs 7.0%, 52 vs 53mmol/mol) and pregnancy outcomes did not differ. Although the numbers of women who conceived are very small, there was a surprising 3kg less gestational weight gain in the CGM group (10.4 vs 13.4kg from confirmed pregnancy to 34 weeks gestation), suggesting that CGM users may have been making substantial dietary adjustments.

Despite all these 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 and but they highlight that despite increased diabetes technology, euglycemia in T1D pregnancy remains elusive before and during pregnancy.

Insulin delivery; pens vs 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 advocating increased 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 (63-140mg/dl), 26% time > 140mg/dl and 3% time < 63mg/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, small sample sizes and not applicable to current clinical practice (32). More recent descriptions are observational and subject to bias and confounding factors (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 non-pregnant UK participants found a mean change in HbA1c at 24 months of −0.8% and −0.4% (-9 and 0.45 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 is 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 minimising glycemic excursions.

Recent developments in CGM accessibility

Whilst 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 to widespread (60%) insulin pump use during 2013-14 (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 forwards. Whilst calibration and some checking of SMBG is still recommended, particularly during hypoglycemia, exercise and driving, both the clinical and the cost-effectiveness of CGM will be greatly enhanced with sensors accurate enough for pre-meal insulin dosing. The longer duration of newer generation sensors, lasting for up to ten days, will benefit users and payers and further improve CGM accessibility.

However, 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 direct to consumers (without the need for physician recommendation) and neither patient nor staff training is required. When it was first introduced in the UK, 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 GDM, 24 type 1 and 11 type 2 diabetes) across 13 sites (9 UK and 4 Austrian) demonstrated that, as expected, sensor accuracy, assessed over 14 days at various gestational ages is comparable (MARD of approximately 12%) in pregnant and non-pregnant users (38). We found that similar agreement between CGM sensor accuracy for pregnant and non-pregnant users of the Navigator sensor when compared to plasma glucose (39). Whilst other sensors may not have specific licenses for use in pregnancy, it seems that accuracy issues are sensor specific and applicable to pregnant and non-pregnant users. The professional version of the Freestyle Libre (available in the USA) will improve the documentation of glycemic profiles in pregnancy. It provides 14-day masked glucose profiles without requiring SMBG, making it an 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 RCTs 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 rapidy 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 HbA1c reductions were most marked (from 8% to 6.7% or 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 and 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 clinicans to determine which patients are candidiates for more advanced CGM, sensor augmented/threshold suspend pump 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, a potential clinical therapeutic reality. A recent systematic review and meta-analyses of 585 participants from 27 outpatient studies found consistent glycemic improvements with 12.6% increased TiR (3 hours/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 was associated with a 15% higher *overnight* time-in-target (75 vs 60%) during T1D pregnancy (41). Preliminary data from this first home closed-loop study, suggest feasibility of *day-and-night* closed-loop throughout pregnancy, including in hospital during labour and delivery. Most women chose to continue closed-loop 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 in T1D pregnancy, found that closed-loop was as effective, but not superior to sensor-augmented pump therapy. Women spent 60% TiR during both interventions in the second trimester, but closed-loop 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% time-in-range (63-140mg/dl) across pregnancy. Women with suboptimal glucose control (HbA1c >7.5% or 53mmol/mol) never caught up and only achieved 65-70% time-in-range 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 post-prandial glucose targets require meticulous attention to carbohydrate estimation and bolusing at least 15-30 minutes before eating (43).

As one in two women with T1D are now entering pregnancy overweight or obese, the importance of optimal dietary intake cannot be overstated (3, 22). Higher pre-pregnancy BMI and higher gestational weight gain, independent of BMI and glycemic control, is associated with increasing neonatal birth weight (44). We found that almost half of the total daily carbohydrate intake of UK participants in the CONCEPTT trial was from "non-recommended" high sugar (biscuits, chocolate, and confectionary) sources. This means that these women, half of whom were overweight or obese before pregnancy, ate approximately 90g per day of "sweet treats". Even the most aggressive closed-loop algorithms and fast-acting insulin analogues cannot safely match these dietary intakes (45). A high-quality dietary intervention trial (of Mediterranean diet or low glycemic index carbohydrates) is as important to guide clinical practice in T1D as in GDM pregnancy. A recent systematic review and metaanalyses found 19 randomised controlled trials of dietary interventions in GDM pregnancy (46). While dietary advice is an essential component of clinical management in T1D pregnancy, there are no high quality dietary interventions and none to guide optimal use of CGM, pumps and closed-loop. Whilst diabetes technology, may add an additional 5-10% time in target range (and possibly more for those with suboptimal glucose control) in T1D pregnancy, addressing maternal dietary intake is imperative to minimise the immediate and longer-term consequences of maternal hypoglycemia.

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Table 1: Changes in mean glucose, HbA1c and percentage of capillary glucose levels >8mmol/L (144mg/dl) during T1D pregnancy.

Gestation	*Mean glucose (mmol/L)*	*HbA1c (%)*	*HbA1c (mmol/mol)*	*% glucose >8mmol/L (140mg/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)

‡ The mean gestational age at booking was 7.2 ±2.2 weeks with 80 (78%) women seen at ≤8 weeks and 90 (88%) at ≤10 weeks.

Table 2: Consensus statement recommendations with suggestions for T1D pregnancy

	Non-pregnant	**Pregnant**
Data sufficiency	70-80% of possible CGM data	70-80% of possible CGM data
Data duration	Miniumum of 2-weeks	Not determined
Time blocks	24hr (midnight to midnight)	24hr (midnight to midnight)
Nighttime	24.00-06.00am	24.00-06.00am or 23.00-07.00hr
Daytime	06.00-24.00	06.00-24.00 or 07.00-23.00hr
Overall control	Mean glucose	Mean glucose
% Time in range (TIR)	70-180mg/dl (3.9-10.0mmol/L)	70-140mg/dl (3.9-7.8mmol/L)
	70-140mg/dl (3.9-7.8mmol/L)	63-140mg/dl (3.5-7.8mmol/L)
Hyperglycaemia – level 1	>180mg/dl (10.0mmol/L)	>140mg/dl (7.8mmol/L)
Hyperglycaemia – level 2	>250mg/dl (13.9mmol/L)	>180mg/dl (10.0mmol/L)
High glucose exposure	High Blood Glucose Index	High Blood Glucose Index
Hypoglycemia – level 1	<70-54mg/dl (3.9-3.0mmol/L)	<70-54mg/dl (3.9-3.0mmol/L) or 63-50mg/dl (3.5-2.8mmol/L)
Hypoglycemia – level 2	<54mg/dl (3.0mmol/L)	<54mg/dl (3.0mmol/L) or <50mg/dl (2.8mmol/L)
Hypoglycemia – level 3	Severe Hypoglycemia	Severe Hypoglycemia
Low glucose exposure	Low Blood Glucose Index	Low Blood Glucose Index
Hypoglycemic event	15 minutes duration	15 minutes duration
Prolonged hypoglycemia	120 minutes	120 minutes
Glycemic variability		
SD	Not reported	<25mg/dl suggested
CV	<36% (stable glycemia)	<36% (stable glycemia)
For research purposes		
Area under the curve (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	HbA1c or TIR and level 2 hypoglycemia	TIR and level 2 hypoglycemia
Broader composite outcomes	HbA1c 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 non-pregnant settings

Table 3: Continuous glucose monitoring (CGM) measures among women in CONCEPTT using insulin pump and multiple daily injections (MDI) during pregnancy

Pump users (N=98)				
	10-11 weeks gestation		**34-35 weeks gestation**	
	CGM	**Control**	**CGM**	**Control**
	N=50	**N=48**	**N=35**	**N=37**
Mean glucose mg/dl	131±22	133±22	121±18	126±16
% Time in target range*	53±12	54±14	66±13	62±14
% Time >140mg/dl	39 (26-47)	39 (29-49)	27 (20-37)	32 (27-41)
% Time < 63mg/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)
CV %	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	**Control**	**CGM**	**Control**
	N=57	**N=59**	**N=42**	**N=40**
Mean glucose mg/dl	131±22	139±18	121±14	126±7.0
% Time in target*	50±13	50±13	69±13	61±17
% Time >140mg/dl	39 (30-49)	41 (34-51)	26 (17-36)	31 (24-39)
% Time < 63mg/dl	8 (5-17)	6 (2-12)	3 (1-6)	5 (2-9)
Hypoglyaemia 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)
CV %	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 mmean ±SD and median (interquartile range) as appropriate.

*Time in target range for T1D pregnancy was defined as 63-140mg/dl (3.5-7.8mmol/L).

¥Hypoglycemia episodes were defined as CGM levels <63mg/dl for at least 20 minutes. Distinct episodes were counted only if separated by at least 30 minutes.

Figure 1: Continuous Glucose Monitoring (CGM) measures of women with T1D during pregnancy in CONCEPTT

1A: Time in T1D pregnancy target range 63-140mg/dl (3.5-7.8mmol/L)

The Home Glucose Monitoring (HGM) control group spent 52% time in target at baseline (12.5 hours/day) rising to 61% (14.6 hours/day) at 34 weeks. The CGM group spent 52% time in target at baseline (12.5 hours/day) rising to 68% (16.3 hours/day) at 34 weeks gestation.

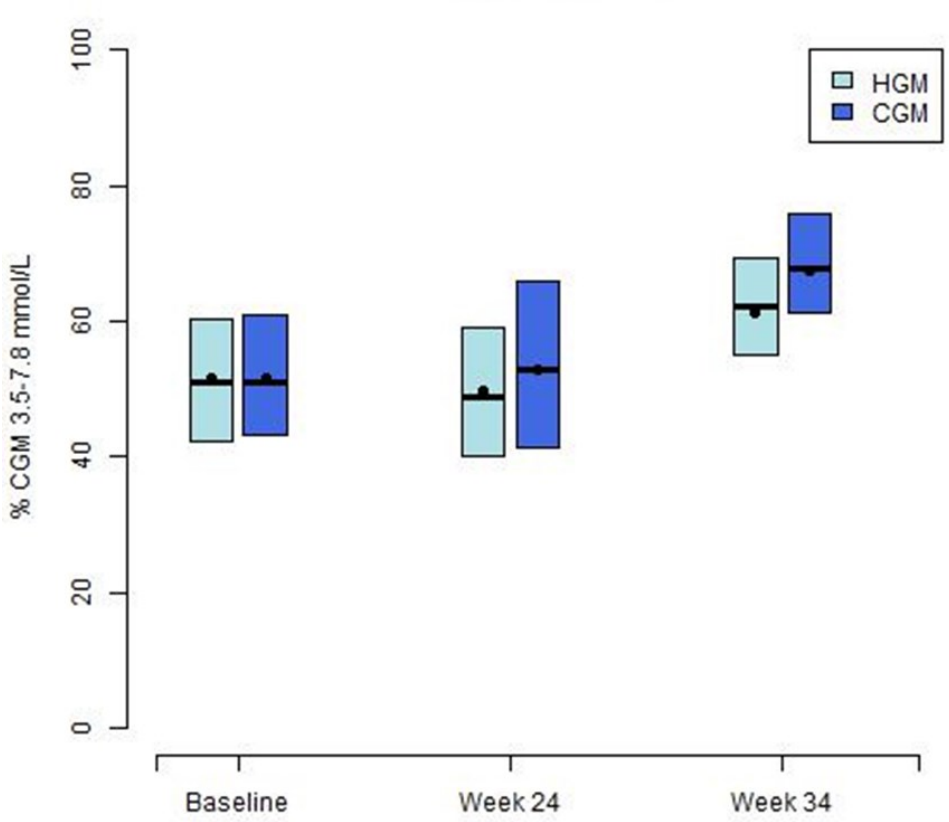

Figure 1b: Time spent hyperglycaemic > 140mg/dl (7.8mmol/L).

The Home Glucose Monitoring (HGM) control group spent 40% time hyperglycaemic at baseline (9.6 hours/day) reducing to 32% (7.7 hours/day) at 34 weeks. The CGM group spent 39% time in target at baseline (9.4 hours/day) reducing to 27% (6.5 hours/day) at 34 weeks gestation; p=0.03.

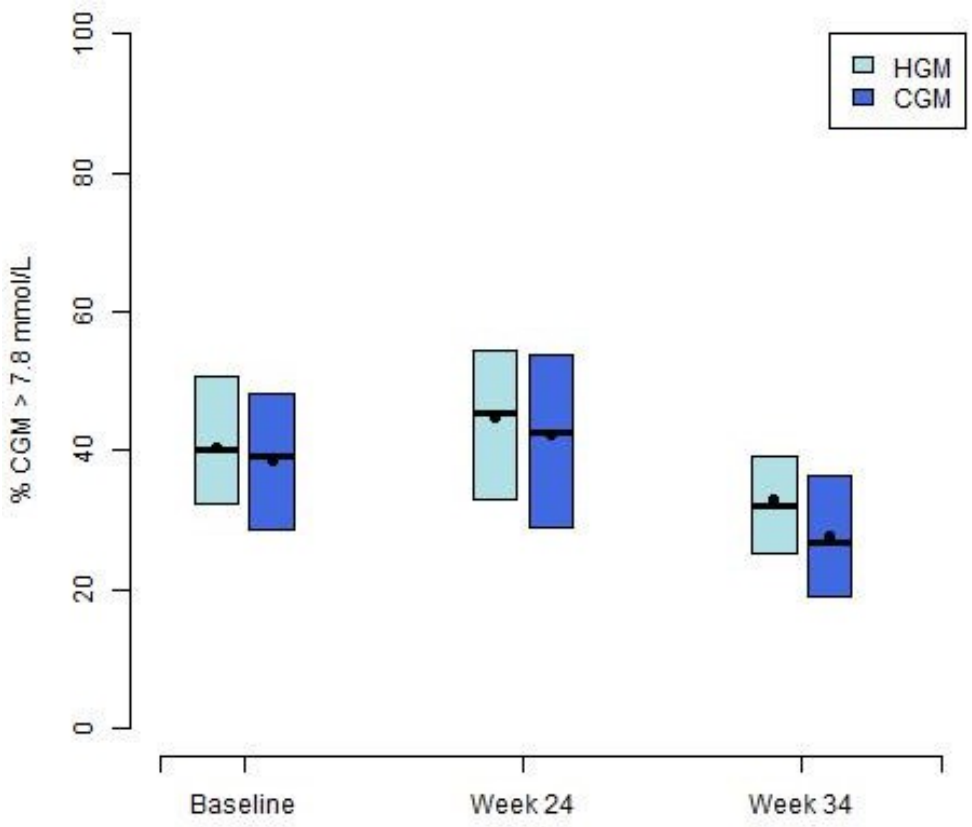

Figure 3: Time spent hypoglycemic < 63mg/dl (3.5mmol/L).

The Home Glucose Monitoring (HGM) control group spent 8% time hyperglycaemic at baseline (1.9 hours/day) reducing to 4% (1.0 hours/day) at 34 weeks. The CGM group spent 6% time in target at baseline (1.4 hours/day) reducing to 3% (0.7 hours/day) at 34 weeks gestation; p=0.10.