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BRIEF REPORT

Continuous Glucose Monitoring Time-in-Range and HbA_{1c} Targets in Pregnant Women with Type 1 Diabetes

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Abstract

The CONCEPTT trial compared real-time Continuous Glucose Monitoring (RT-CGM) to capillary glucose monitoring in pregnant women with type 1 diabetes. We analyzed CGM and glycated hemoglobin (HbA_{1c}) measures in first ($n=221$), second ($n=197$), and third ($n=172$) trimesters, aiming to examine target glucose attainment and associations with pregnancy outcomes. CGM targets were Time-in-range (TIR) >70%, Time-above-range (TAR) <25%, and Time-below-range (TBR) <4%, and HbA_{1c} targets <6.5% (National Institute for Health and Care Excellence [NICE]) and HbA_{1c} <6.0% in second and third trimesters (American Diabetes Association [ADA]). TIR/TAR/TBR targets were achieved by 7.7/14.5/30.3% participants in first, 10.2/14.2/52.8% in second, and 35.5/37.2/52.9% in third trimesters. CGM target attainment was low but increased during pregnancy and with RT-CGM use. In the adjusted analyses, achieving TBR target was associated with a higher risk of pre-eclampsia and neonatal hypoglycemia. ADA HbA_{1c} target attainment was low and unchanged during pregnancy (23.5/27.9/23.8%) but increased with RT-CGM use. In the adjusted analyses, HbA_{1c} target attainment was associated with a lower risk of preterm birth, large-for-gestational age and neonatal hypoglycemia. We conclude that CONCEPTT trial participants had a low rate of CGM and of HbA_{1c} target attainment. Attainment of CGM and NICE HbA_{1c} targets increased throughout gestation and all targets (both NICE/ADA HbA_{1c} and CGM) were more likely to be achieved by RT-CGM users, at 34 weeks' gestation. ADA HbA_{1c} target achievement was independently associated with better perinatal outcomes, while the independent association of

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*See Supplementary Appendix A1.

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Introduction

Standardized continuous glucose monitoring (CGM) metrics and glycated hemoglobin (HbA_{1c}) are recommended for monitoring glucose in people with diabetes.[1] The international consensus on Time-in-range (TIR) for CGM data interpretation was published in 2019.[2] The recommended percentages of glucose readings in the target range for pregnant women with type 1 diabetes mellitus (T1D) were >70% time (16 h, 48 min) for TIR of 3.5–7.8 mmol/L (63–140 mg/dL), <25% time (6 h) for Time-above-range (TAR) of >7.8 mmol/L (>140 mg/dL), and <4% time (1 h) for Time-below-range (TBR) of <3.5 mmol/L (<63 mg/dL). These values were based on the CONCEPTT trial[3] and a cohort study.[4]

CONCEPTT was a randomized controlled trial, which included 215 pregnant women and 110 women planning pregnancy, assigned to real-time CGM (RT-CGM) in addition to capillary glucose monitoring or capillary glucose monitoring alone (plus 6-day masked CGM in early, mid, and late gestation).[3] Pregnant RT-CGM users had improved glucose control (HbA_{1c}, TIR, and TAR at 34 weeks) and pregnancy outcomes (infants large-for-gestational age [LGA], with neonatal hypoglycemia requiring intravenous dextrose or admission to neonatal intensive care unit [NICU] longer than 24 h). The cohort study included 186 pregnant women with T1D using RT-CGM or intermittent monitoring.[4] In both studies, a higher TIR was associated with a reduced risk of LGA. Each 5% increase in TIR was associated with benefits for neonatal outcomes.[5]

In turn, HbA_{1c} is well recognized as the traditional gold standard of glycemic control and biomarker of maternal and neonatal complications.[6] Nevertheless, HbA_{1c} has limitations outside and during pregnancy, since its results can be affected by factors such as ethnicity,[1,7] age,[8] and erythrocyte disorders.[9–11] HbA_{1c} targets for pregnant women with T1D are <6.5% (48 mmol/mol) before and throughout pregnancy as recommended by the National Institute for Health and Care Excellence (NICE)[12] and <6.5% (48 mmol/mol) before pregnancy/first trimester and <6.0% (42 mmol/mol) in second and third trimesters as recommended by the American Diabetes Association (ADA).[6] Although we have studied TIR and HbA_{1c} in this population, we have not addressed attaining the recommended goals.[13]

The main objective of this subanalysis was to examine CGM-based and ADA HbA_{1c} target glucose attainment in pregnant women participating in the CONCEPTT trial. As a secondary objective, we aimed to evaluate the associations between CGM and HbA_{1c} target attainment with pregnancy outcomes.

Materials and Methods

All centers received ethical approval. All participants gave written informed consent. The current study derives from a pre-specified secondary analysis approved by the CONCEPTT trial steering committee before trial completion.

CGM measurements and blood sampling were performed as detailed in the study protocol.[14] We analyzed 6-day CGM readings (Guardian REAL-Time or MiniMed Minilink System, Medtronic, Northridge, CA in the intervention group and masked iPro2 Professional CGM, Medtronic, Northridge, CA, USA, in the control group) at first trimester, 24, and 34 weeks' gestation. HbA_{1c} measures were taken at the same three time points. After delivery, HbA_{1c} samples were measured in the central laboratory (DynaCare, Brampton, ON, Canada) using the turbidimetric inhibition immunoassay for hemolyzed whole blood on the Cobas Integra 700 platform (Roche, Basel, Switzerland).[3] Women were included if both CGM and HbA_{1c} data were available at the study time points. The primary outcome addressed was percentage of women achieving the proposed CGM (TIR, TAR, and TBR) and HbA_{1c} targets as already defined, at the three time points. The outcomes tested versus CGM and HbA_{1c} target attainment were pre-eclampsia, cesarean section, preterm birth, LGA, neonatal hypoglycemia, and NICU admission.

We performed descriptive statistics to characterize the group and chi-square and nonparametric tests for bivariate comparisons (Mann–Whitney/Kruskal–Wallis tests). Logistic regression analysis was used to estimate the ability of CGM and HbA_{1c} target attainment in each trimester to predict pregnancy outcomes. A second set of models weas adjusted by age, body mass index (BMI), duration of T1D, ethnicity, parity, center, randomization arm, preconception planning, and smoking habit. No imputations were used. Significance was set at $P < 0.05$. Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

The potential study population was 249 women, the 215 participants enrolled in the pregnancy trial and the 34 women in the planning pregnancy trial who became pregnant. Women included in this subanalysis were 221 at baseline, 197 at 24 weeks, and 172 at 34 weeks; corresponding figures for maternal and neonatal outcomes for women delivering a live birth at ≥20 weeks were 204, 196, and 171. The characteristics of included women were mean age 31.5 years, BMI 25.8 kg/m^2, T1D duration 16.8 years, gestational age at randomization/pregnancy confirmation 10.2 weeks and baseline HbA_{1c} 6.9% (52 mmol/mol) (Supplementary Table S1, very similar to all pregnant CONCEPTT participants).

Figure 1 displays average TIR, TAR, TBR, and HbA_{1c} in each trimester, P-values for change over time were $P < 0.001$ for all metrics. Table 1 gives the proportion of women who reached the recommended CGM-based and HbA_{1c} targets in each trimester. Overall, the rate of CGM target attainment increased during pregnancy. At 34 weeks, the percentage of women achieving TIR, TAR, and TBR targets was higher in the RT-CGM group than in the control group. The percentage of women fulfilling none of the CGM targets was 53.8% at baseline, 32% at 24 weeks, and 5.8% at 34 weeks. The simultaneous attainment of the three CGM targets was 2.7%, 2%, and 17% respectively.

CGM metrics according to HbA_{1c} target attainment at the three time points were for HbA_{1c} <6.5%: TIR 60%/57%/

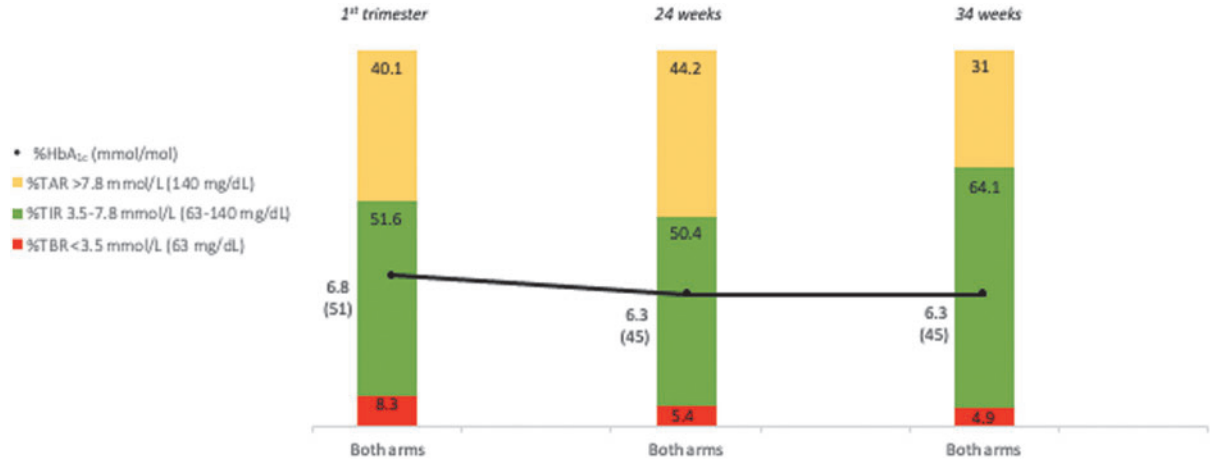

FIG. 1. CGM-based TIR and HbA_{1c} in pregnant women included in the subanalysis. The diagram displays average TIR, TAR, TBR, and HbA_{1c} in each trimester for RT-CGM and control arms combined. *P*-values for change over time were $P < 0.001$ for TAR, $P < 0.001$ for TIR, $P < 0.001$ for TBR, and $P < 0.001$ for HbA_{1c}. CGM, continuous glucose monitoring; HbA_{1c}, glycated hemoglobin; RT-CGM, real-time CGM; TAR, Time-above-range; TBR, Time-below-range; TIR, Time-in-range. Color graphics appear online.

69.3%, TAR 31%/37.3%/25.3%, and TBR 7%/5%/4%, and for HbA_{1c} <6%: TIR 67.3%/61.4%/71.9%, TAR 16%/32%/22.6%, and TBR 7%/5.2%/4.2%.

Table 1 also gives the rates of women attaining HbA_{1c} targets in each trimester (ADA period-specific goals, <6.5% [48 mmol/mol] and <6.0% [42 mmol/mol]). The percentage of women with HbA_{1c} <6.5% (48 mmol/mol) and <6.0% (42 mmol/mol) increased during pregnancy but the proportion of those achieving period-specific goals did not change. However, RT-CGM and control groups differed at 34 weeks in the frequency of HbA_{1c} target attainment (31% vs. 17%, $P = 0.032$) due to a nonsignificant increase in RT-CGM group and a nonsignificant decrease in the control group.

Pregnancy outcomes were as follows: 13.1% pre-eclampsia, 67% cesarean section, 40.3% preterm birth, 61.3% LGA, 24.5% neonatal hypoglycemia, and 37.3% NICU admission.

Associations for target attainment with pregnancy outcomes are displayed in Supplementary Table S2. Achieving the TIR target at 34 weeks was associated with a lower risk of preterm birth, achieving the TAR target at 24 weeks was associated with a lower risk of LGA, and achieving the TAR target at 34 weeks was associated with a lower risk of both LGA and preterm birth. In contrast, achieving the TBR target at 24 weeks was associated with an increased risk of neonatal hypoglycemia and NICU admission. Regarding HbA_{1c}, a value <6.5% (48 mmol/mol) in

Table 1. Continuous Glucose Monitoring and Glycated Hemoglobin Target Attainment During Type 1 Diabetes Pregnancy

Type 1 diabetes pregnancy glucose targets	*Percentage of women fulfilling glucose targets*			
	First trimester (N = 221) Both arms RT-CGM versus control	*24 Weeks (N = 197) Both arms RT-CGM versus control*	*34 Weeks (N = 172) Both arms RT-CGM versus control*	P-*value for change over time for both arms for RT-CGM, for control arm*
CGM				
TIR 3.5–7.8 mmol/L	7.7	10.2	35.5	<0.001
(63–140 mg/dL) >70%	6.2 versus 9.3[ns]	10.5 versus 9.8[ns]	44.0 versus 27.3[a]	<0.001, <0.001
TAR >7.8 mmol/L	14.5	14.2	37.2	<0.001
(>140 mg/dL) <25%	15.9 versus 13[ns]	16.8 versus 11.8[ns]	46.4 versus 28.4[a]	<0.001, <0.01
TBR <3.5 mmol/L	30.3	52.8	52.9	<0.001
(<63 mg/dL) <4%	26.5 versus 34.3[ns]	53.7 versus 52[ns]	63.1 versus 43.2[b]	<0.001, <0.05
Laboratory				
ADA trimester-specific	23.5	27.9	23.8	ns
HbA_{1c} target	23.0 versus 24.1[ns]	30.5 versus 25.5[ns]	31.0 versus 17.0[a]	ns, ns
NICE HbA_{1c} target	23.5	59.4	54.1	<0.001
<6.5% (48 mmol/mol)	23.0 versus 24.1[ns]	65.3 versus 53.9[ns]	63.1 versus 45.5[a]	<0.001, <0.001
HbA_{1c} <6.0% (42 mmol/mol)	3.6	27.9	23.8	<0.001
	2.7 versus 4.6[ns]	30.5 versus 25.5[ns]	31.0 versus 17.0[a]	<0.001, <0.001

ADA indicates HbA_{1c} <6.5% (48 mmol/mol) as prepregnancy target and <6.0% (42 mmol/mol) in the second and third trimesters.
P value RT-CGM versus control: [a]<0.05; [b]<0.01.
ADA, American Diabetes Association; CGM, continuous glucose monitoring; HbA_{1c}, glycated hemoglobin; NICE, National Institute for Health and Care Excellence; NS, nonsignificant; RT-CGM, real-time CGM; TAR, Time-above-range; TBR, Time-below-range; TIR, Time-in-range.

the first trimester was associated with a lower risk of LGA. An HbA_{1c} < 6.0% (42 mmol/mol) at 24 weeks was associated with a lower risk of preterm birth, LGA, neonatal hypoglycemia, and NICU admission; an HbA_{1c} < 6.0% (42 mmol/mol) at 34 weeks was associated with a lower risk of preterm birth, LGA and neonatal hypoglycemia.

After adjustment for clinical variables, attaining TBR target in the first trimester was associated with an increased risk of preeclampsia, and with increased risk of neonatal hypoglycemia at 24 weeks. For HbA_{1c}, attaining ADA trimester-specific target in first trimester was associated with a reduced risk of LGA, with reduced risk of both preterm birth and neonatal hypoglycemia at 24 weeks, and preterm birth at 34 weeks.

Discussion

In this subanalysis, we observed that CONCEPTT trial participants had a low rate of CGM TIR target attainment that increased during pregnancy and peaked at 44% of women in the RT-CGM group at 34 weeks. Similarly, rates of HbA_{1c} below the ADA cutoff for each trimester were achieved in less than one-third of women, were unchanged during pregnancy, and highest in the RT-CGM group at 34 weeks.

In the unadjusted analyses, achieving TIR and especially TAR targets at 24 and 34 weeks was associated with better perinatal outcomes in terms of preterm birth and LGA. However, TBR target attainment was associated with a higher risk of neonatal hypoglycemia and NICU admission. Achieving ADA HbA_{1c} trimester-specific targets was associated with better neonatal outcomes in all trimesters (LGA in the first, four outcomes at 24 weeks, and three outcomes at 34 weeks).

In the adjusted analyses, achieving ADA HbA_{1c} trimester-specific targets was independently associated with better perinatal outcomes. However, for CGM targets, the only significant associations were for increased risk in association with attainment of TBR target. This could be attributed to the fact that most women achieving <4% TBR did not achieve TIR or TAR targets, but adjusted odds ratios for TIR and TAR do not support this interpretation. An alternative hypothesis is that spending more time at low glucose values is associated with better neonatal outcomes. The lower TBR cutoff in pregnant women is due to glucose levels being physiologically lower during pregnancy. In fact, data from healthy pregnant women indicate that rates of glucose readings <3.5 mmol/L (<63 mg/dL) are higher than 4%.[15,16] The association between TBR targets and pregnancy outcomes warrants further study with newer generation CGM sensors with improved accuracy in the lower glucose range. In addition to carefully balancing the maternal risks of severe hypoglycemia in women with T1D with potential neonatal benefits, modification of current TBR cutoffs would require tools to safely bring glucose to low values.

A strength of these results is that they provide evidence from a well-designed multicenter international trial. Notably, to our knowledge, this subanalysis is the first to compare the attainment of CGM-based targets using TIR International Consensus Report with HbA_{1c} targets in pregnant women with T1D. However, some limitations are worth noting. First, we only analyzed 6-day CGM readings; associations of CGM metrics with perinatal outcomes could have been more robust if they had been measured throughout pregnancy, but this would have limited the analysis to the RT-CGM group. Second, as trial criteria for pregnancy enrolment excluded women with first pregnancy HbA_{1c} <6.5% (48 mmol/mol) or at enrolment >10.0% (86 mmol/mol), our observations do not include the whole spectrum of glycemia in early pregnancy.[14]

The rates of CGM target attainment were low and despite their increase throughout gestation, peak targets were only achieved by 44% of women for TIR, 46.4% for TAR, and 63.1% for TBR at 34 weeks in the RT-CGM group. Similarly, rates of HbA_{1c} below the ADA cutoff for each trimester were achieved in less than one third of women, and even when they did not increase significantly during pregnancy, the rate of HbA_{1c} <6.0% (42 mmol/mol) was higher at 34 weeks in the RT-CGM group. According to the proportion of women attaining different targets, TIR and TAR targets were more stringent than HbA_{1c} <6.5% (48 mmol/mol) throughout pregnancy, whereas for HbA_{1c} <6.0% (42 mmol/mol), it depended on the trimester. ADA HbA_{1c} target achievement was superior to 6-day CGM measures in the prediction of pregnancy outcomes, reflecting the fact that HbA_{1c} is a measure of average glucose over a 2–3-month period.[17] Other studies have addressed CGM metrics and/or HbA_{1c} in pregnant women with pregestational diabetes but not target attainment for both biomarkers.[18–21]

In clinical practice, to minimize complications attributable to fetal hyperinsulinism, efforts aim at achieving and sustaining maternal glucose in the target range throughout pregnancy. Our results suggest that, even when RT-CGM has been shown to improve clinical outcomes, additional improvement is required for women to reach the tight CGM TIR and ADA HbA_{1c} targets before late gestation. Possible solutions may include better pre-pregnancy planning, lifestyle changes, as well as treatment and technological advances. Preliminary data suggest that interventions such as closed-loop systems may be beneficial for supporting pregnant women with T1D to safely achieve higher TIR and lower TAR.[22,23]

Conclusions

In conclusion, CONCEPTT trial participants had a low rate of CGM and of HbA_{1c} target attainment especially for the trimester-specific ADA HbA_{1c} targets, which were unchanged during pregnancy. Attainment of CGM and NICE HbA_{1c} targets increased throughout gestation and all targets (both NICE/ADA HbA_{1c} and CGM) were more likely to be achieved by RT-CGM users, at 34 weeks' gestation. ADA HbA_{1c} target achievement was independently associated with better perinatal outcomes, whereas the independent association of TBR target achievement with increased risk warrants further study.

Authors' Contributions

D.T. analyzed and interpreted the data and wrote the article. C.L.M., J.Y., and C.M.-B. contributed to the analysis, interpretation, and discussion of the data. I.G. contributed to the statistical analysis and interpretation of the data. D.S.F. contributed to the interpretation and discussion of the data. H.R.M. identified the study question and contributed to the interpretation and discussion of the data. R.C. designed the study, analyzed and interpreted the data, and revised the article. All authors reviewed the final version of the article before publication.

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Author Disclosure Statement

D.T., C.L.M., J.Y., C.M.-B., and I.G. have no relevant conflicts of interest to report. D.S.F. has received honoraria for speaking engagements from Medtronic and has been on an advisory board for Novo Nordisk. H.R.M. has received honoraria for speaking engagements from Medtronic, Roche, Novo Nordisk, and Eli Lilly and is a member of the Medtronic European Advisory Board. R.C. has received honoraria for speaking engagements with Eli Lilly and Novo Nordisk and has been on an advisory boards for Novo Nordisk and Abbott.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Appendix SA1

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