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Continuous glucose monitoring metrics and pregnancy outcomes in insulin-treated diabetes: A post-hoc analysis of the GlucoMOMS trial

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Abstract

Aim: To investigate the association between continuous glucose monitoring (CGM) metrics and perinatal outcomes in insulin-treated diabetes mellitus in pregnancy.

Materials and Methods: In a post-hoc analysis of the GlucoMOMS randomized controlled trial, we investigated the association between the metrics of an offline, intermittent CGM, glycated haemoglobin (HbA1c) and perinatal outcomes per trimester in different types of diabetes (type 1, 2 or insulin-treated gestational diabetes mellitus [GDM]). Data were analysed using multivariable binary logistic regression. Outcomes of interest were neonatal hypoglycaemia, pre-eclampsia, preterm birth, large for gestational age (LGA) and Neonatal Intensive Care Unit (NICU) admission. The glucose target range was defined as 3.5–7.8 mmol/L (63–140 mg/dL).

Results: Of the 147 participants (N = 50 type 1 diabetes, N = 94 type 2 diabetes/insulin-treated GDM) randomized to the CGM group of the GlucoMOMS trial, 115 participants had CGM metrics available and were included in the current study. We found that, in pregnancies with type 1 diabetes, a higher second trimester mean glucose was associated with LGA (odds ratio 2.6 [95% confidence interval 1.1–6.2]). In type 2 and insulin-treated gestational diabetes, an increased area under the curve above limit was associated with LGA (odds ratio 10.0 [95% confidence interval 1.4–72.8]). None of the CGM metrics were associated with neonatal hypoglycaemia, pre-eclampsia, shoulder dystocia, preterm birth and NICU admission rates for pregnancies complicated by any type of diabetes.

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Conclusion: In this study, in type 2 diabetes or insulin-treated GDM, the glucose increased area under the curve above limit was associated with increased LGA. In type 1 diabetes, the mean glucose was the major determinant of LGA. Our study found no evidence that other CGM metrics determined adverse pregnancy outcomes.

KEYWORDS
continuous glucose monitoring, diabetes in pregnancy, gestational diabetes, large-for-gestational age

1 | INTRODUCTION

Diabetes is the most common metabolic disorder of pregnancy, affecting up to one in six pregnancies worldwide.[1] Diabetes in pregnancy is associated with adverse perinatal outcomes, including large for gestational age (LGA), pre-eclampsia and neonatal hypoglycaemia. Optimal maternal glycaemic control is fundamental in minimizing the risk of perinatal complications.[2]

Since its introduction, continuous glucose monitoring (CGM) has seen rapid uptake in diabetes-related pregnancy. CGM use in relation to pregnancy outcomes has been primarily investigated in women with type 1 diabetes.[3-7] A Swedish observational cohort study of 186 pregnancies in type 1 diabetic women showed that the lower time in range (TIR) and higher time above range (TAR) during the second and third trimesters predicted LGA.[6] The CONCEPTT randomized trial showed that real-time CGM use led to a lower incidence of LGA, and a reduced rate of neonatal hypoglycaemia and neonatal intensive care unit (NICU) admission compared with capillary glucose measurements.[3] Guidelines have since recommended real time-CGM in all pregnancies complicated by type 1 diabetes, recommendations regarding which CGM metrics to use to guide therapy are consensus based; in line with its use outside pregnancy, TIR is the metric suggested to be of most relevance for perinatal outcomes.[8,9] Following the introduction for CGM, initially only in type 1 diabetes, CGM is now increasingly being employed in women with type 2 diabetes and gestational diabetes mellitus (GDM). However, CGM metrics and their associations with perinatal outcome in GDM and type 2 diabetes pregnancies have, to our knowledge, not been evaluated. The current study explores the association between CGM metrics collected in the GlucoMOMS trial to pregnancy outcomes in different types of diabetes.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The current study is a post-hoc analysis of the GlucoMOMS multicentre randomized controlled trial, which studied the effect of

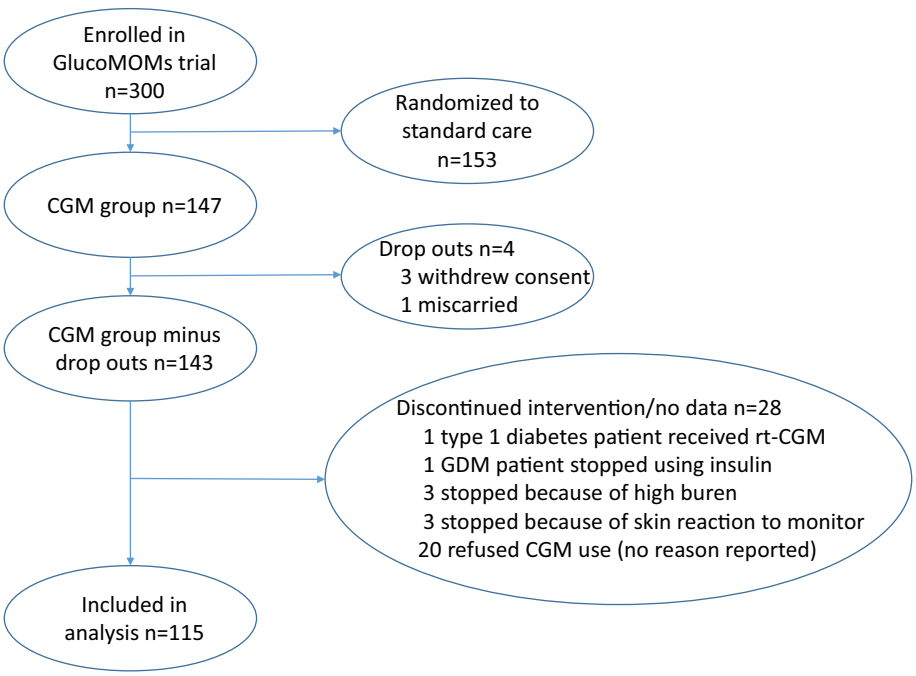

FIGURE 1 Study flow of eligibility of the secondary analysis of the GlucoMOMS trial. CGM, continuous glucose monitoring.

offline CGM during insulin-treated diabetic pregnancy.[10] The study protocol of the multicentre GlucoMOMS trial has been published previously.[11] Briefly, enrolment in the trial took place from July 2011 to September 2015. The study protocol was approved by the ethics committee of the Academic Medical Center Amsterdam (reference number MEC AMC 10/322). All participants gave written informed consent, including for the use of CGM data for scientific purposes. The trial investigated whether the use of intermittent retrospective CGM in a composite group of insulin-treated type 1 diabetes, type 2 diabetes and insulin-treated GDM affected pregnancy outcomes, primarily macrosomia.[10] The GlucoMOMS trial found no benefit of intermittent retrospective CGM on perinatal outcomes.

GlucoMOMS included participants with pre-existing diabetes mellitus (type 1 or 2) with insulin treatment before 16 weeks of pregnancy or insulin-treated GDM, defined as necessitating the initiation of insulin treatment before 30 weeks of gestational age. Included participants were randomized to the CGM group (intervention) or the standard care group, stratified according to type of diabetes. At the time the trial was conducted, standard care consisted of self-monitoring of blood glucose (SMBG).

The CGM study arm of the GlucoMOMS trial received intermittent retrospective CGM, also referred to as offline CGM, in addition to standard care. Patients were not able to see the glucose measurements while wearing the CGM sensor. Thus, for day-to-day self-management of glycaemic control participants used their SMBG results. CGM metrics were evaluated by the local endocrinologist directly after a CGM cycle (5–7 days of monitoring) and changes in diet or insulin dosing schedule were advised according to the clinical appraisal of the treating endocrinologist.[11] Patients received obstetric and diabetes care as appropriate, according to local protocols and national guidelines.

For this post-hoc analysis, only participants randomized to the CGM group having completed at least one CGM cycle of at least five consecutive days of monitoring were eligible for inclusion.

The datasets generated during and/or analysed in the current study are available from the corresponding author upon reasonable request.

2.2 | Data collection

Baseline characteristics of participants, glycated haemoglobin (HbA1c) levels and neonatal and maternal outcomes were collected from patients' routine care charts or electronic health records. HbA1c measurements were categorized per trimester. If more than one HbA1c measurement was available per trimester, the measurement nearest to 12 ± 4, 24 ± 5 or 34 ± 5 weeks was used for the analyses.

A CGM sensor (iPro2; Medtronic) was used to assess glucose levels, retrospectively using Carelink iPro Therapy Management Software for Diabetes to upload readings and present the readings graphically (Figure S1).[10] Depending on the gestational age at inclusion, participants would complete a CGM cycle at about 12, 18, 24, 30 and 36 weeks gestational age.[11] CGM metrics collected at 12 weeks gestational age were referred to as first trimester measurements. Second trimester measurements were computed as the mean of week 18 and 24 if both are available, or one of the two values if otherwise. The same applied to third trimester measurements at 30 and 36 weeks gestational age.

2.3 | Continuous glucose monitoring derived metrics of glycaemic control

We calculated the following CGM metrics: TIR (%) defined as glucose concentrations between 3.5 and 7.8 mmol/L (63 and 140 mg/dL);

TABLE 1 Demographics and characteristics of included participants. according to type of diabetes (type 1 diabetes or type 2 diabetes and GDM)

Characteristic	Type 1 diabetes (n = 42)	Type 2 diabetes and GDM (n = 73)
Demographics		
Age, years	**31 ± 5**	**33 ± 5**
Native-Dutch origin	**36 (84)**	**46 (64)**
Nulliparous	**25 (58)**	**24 (33)**
Pregestational body mass index, kg/m^2	**26 ± 5**	**31 ± 7**
Gestational age at enrolment, days	166 ± 89	138 ± 66
Preconception folic acid use	21 (49)	39 (54)
Diabetes and treatment		
Duration of diabetes, years[a]	**10 ± 7**	**4 ± 4**
Preconception HbA1c, mmol/mol[a]	55 ± 15	50 ± 17
Insulin treatment before gestation[b]	-	34 (47)
Gestational age at GDM diagnosis, days[c]	-	146 ± 45)
Pregnancy outcome		
Neonatal hypoglycaemia	**24 (57)**	**22 (32)**
Large for gestational age, >90th centile	**18 (42)**	**15 (21)**
Preterm delivery, <37 weeks	11 (26)	12 (17)
Pre-eclampsia	1 (2)	3 (4)
Caesarean section	9 (27)	11 (19)
NICU admission	8 (20)	14 (21)

Note: Data are presented as mean ± SD or count (%). Statistically significant differences between groups are displayed in bold characters ($p < .05$).
Abbreviations: GDM, gestational diabetes mellitus; HbA1c, haemoglobin A1C; NICU, neonatal Intensive Care Unit.
[a]Only applicable for cases with type 1 and type 2 diabetes.
[b]Only applicable for cases with type 2 diabetes.
[c]Only applicable for cases with GDM.

time above target range (TAR, %), defined as glucose levels above 7.8 mmol/L (140 mg/dL); time below target range (TBR, %) defined as glucose levels under 3.5 mmol/L (63 mg/dL) and mean glucose.[3] In addition, as advised by International Consensus on CGM, we calculated area under the curve above limit (AUCal), the AUC of glucose levels above the upper limit of the target range (7.8 mmol/L, 140 mg/mL), as shown in Figure S2.[12] This was calculated as the definite integral of the curve that reflects variations in glucose levels (amplitude) as a function of time. The AUCal provides an index for the combination of TAR and the amplitude of glucose excursions (i.e. severity) representing both the x-axis and y-axis of graphically displayed CGM.[13] The AUCal therefore gives comprehensive information as it indicates overall extent and duration of glucose excursions. Most other CGM metrics provide a simplified representation of glycaemic control, reflecting either the x-axis (time; TIR, TAR and TBR) or the y-axis (glucose level; mean glucose and glucose SD).

2.4 | Outcome measures

Outcomes included are according to the core outcome set of pregnant women with pregestational diabetes[14]; neonatal hypoglycaemia,

TABLE 2 CGM metrics and HbA1c in the first, second and third trimester

Type 1 diabetes	First trimester (n = 18)	Second trimester (n = 36)	Third trimester (n = 33)
TIR, %	57 ± 15	59 ± 15	66 ± 16
TAR, %	30 ± 18	29 ± 18	28 ± 18
TBR, %	12 ± 10	8 ± 8	7 ± 8
Mean glucose, mmol/L	6.3 ± 1.0	6.8 ± 1.4	6.8 ± 1.2
AUCal, mmol/L	0.8 ± 0.7	0.8 ± 0.7	0.6 ± 0.5
HbA1c, mmol/mol	43 ± 4	43 ± 7	46 ± 8
Type 2 diabetes	**(n = 17)**	**(n = 29)**	**(n = 26)**
TIR, %	63 ± 20	65 ± 16	65 ± 14
TAR, %	32 ± 20	30 ± 18	32 ± 20
TBR, %	5.2 ± 7.0	5.2 ± 5.7	4.8 ± 4.3
Mean glucose, mmol/L	6.2 ± 1.0	6.0 ± 0.9	6.0 ± 0.8
AUCal, mmol/L	0.4 ± 0.4	0.3 ± 0.4	0.3 ± 0.3
HbA1c, mmol/mol	43 ± 9	39 ± 6	43 ± 8
Insulin-treated GDM	**(n = 0)**	**(n = 17)**	**(n = 38)**
TIR, %	-	74 ± 13	78 ± 20
TAR, %	-	24 ± 13	20 ± 20
TBR, %	-	2.4 ± 2.7	2.1 ± 3.1
Mean glucose, mmol/L	-	5.7 ± 0.6	5.9 ± 1.0
AUCal, mmol/L	-	0.1 ± 0.1	0.2 ± 0.5
HbA1c, mmol/mol	-	37 ± 8	39 ± 6
Total	**(n = 35)**	**(n = 82)**	**(n = 97)**
TIR, %	63 ± 20	73 ± 19	77 ± 18
TAR, %	27 ± 21	22 ± 20	18 ± 17
TBR, %	9 ± 9	6 ± 6	5 ± 6
Mean glucose, mmol/L	6.4 ± 1.2	6.4 ± 1.1	6.2 ± 1.0
AUCal, mmol/L	0.6 ± 0.6	0.5 ± 0.6	0.4 ± 0.5
HbA1c, mmol/mol	43 ± 8	40 ± 8	44 ± 9

Note: Data are presented as mean ± SD.

Abbreviations: AUCal, area under the curve above limit, which is AUC of glucose levels above 7.8 mmol/L; CGM, continuous glucose monitoring; glucose SD, standard deviation of the mean glucose concentrations; HbA1c, glycated haemoglobin; mean glucose, average glucose concentration calculated over the total period of time with CGM output; TAR, time spent above the upper limit of the glucose target range (>7.8 mmol/L) expressed as the percentage of the total period of time with CGM output; TBR, time spent below the lower limit of the glucose target range (<3.5 mmol/L) expressed as the percentage of the total period of time with CGM output; TIR, time spent in glucose target range of 3.5–7.8 mmol/L expressed as the percentage of the total period of time with available CGM output.

defined as a BG level <2.6 mmol/L (46 mg/dL) within the first 48 h after birth, LGA (birth weight above the 90th centile adjusted for gestational age), pre-eclampsia (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in a previously normotensive woman and proteinuria of ≥300 mg per 24 h; either de novo or superimposed on pre-existent hypertension), preterm birth (<37 weeks of gestation) caesarean section, shoulder dystocia and NICU admission. In addition, we included birth weight in z-score as a continuous outcome.

2.5 | Statistics

Continuous variables were described as mean ± SD and categorical variables in numbers and frequencies (%). Potential differences in clinical characteristics between eligible and non-eligible participants allocated to CGM in the original GlucoMOMS trial were assessed using a t-test for continuous variables and a Pearson chi-squared test or Fisher's exact test for dichotomous variables.

To assess potential association between CGM metrics (TIR; TAR; TBR; mean glucose; AUCal) and HbA1c with pregnancy outcomes, we used adjusted binary logistic regression models and for birth weight in z-score a linear regression model. The models were adjusted for potential confounding by maternal age, pre-pregnancy body mass index and ethnicity. The analyses of potential relationships with neonatal hypoglycaemia were also adjusted for gestational age at birth. Type 1 diabetes was analysed separately from type 2 diabetes and insulin-treated GDM owing to the vast differences in pathophysiology, which we hypothesized could impact the size and strength of associations between CGM metrics and perinatal outcome. Women with type 2 diabetes and insulin-treated GDM were pooled because

TABLE 3A Glycaemic variables and their relationship with pregnancy outcomes in women with type 1 diabetes (n = 42)

	Neonatal hypoglycaemia (n = 13) OR (95% CI)	Large for gestational age (n = 12) OR (95% CI)	Preterm birth (<37 weeks gestational age) (n = 6) OR (95% CI)	NICU admission (n = 4) OR (95% CI)
First trimester				
TIR, %	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.1 (0.6–4.1)	1.1 (0.9–1.3)
TAR, %	1.0 (1.0–1.1)	1.1 (1.0–1.2)	0.9 (0.8–1.0)	0.9 (0.7–1.1)
TBR, %	1.0 (0.9–1.1)	0.8 (0.5–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.3)
Mean glucose, mmol/L	1.2 (0.5–3.0)	4.2 (0.8–22.4)	0.4 (0.1–1.7)	0.5 (0.0–4.9)
AUCal, mmol/L	1.4 (0.3–7.5)	2.3 (0.5–10.8)	0.2 (0.0–2.0)	0.4 (0.0–7.9)
HbA1c, mmol/mol	1.1 (1.0–1.3)	0.9 (0.8–1.1)	1.1 (0.9–1.2)	1.0 (0.8–1.2)
Second trimester				
TIR, %	0.9 (0.9–1.0)	0.9 (0.9–1.1)	0.9 (0.9–1.0)	1.1 (0.9–1.1)
TAR, %	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (0.9–1.1)
TBR, %	1.0 (0.9–1.2)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	1.0 (0.8–1.2)
Mean glucose, mmol/L	0.9 (0.4–1.8)	**2.6 (1.1–6.2)**	0.4 (0.1–1.7)	0.9 (0.3–2.5)
AUCal, mmol/L	0.6 (0.2–1.7)	2.4 (0.8–7.2)	1.6 (0.5–4.9)	0.5 (0.1–3.5)
HbA1c, mmol/mol	1.1 (1.0–1.2)	1.0 (0.9–1.0)	1.1 (1.0–1.1)	1.0 (0.8–1.1)
Third trimester				
TIR, %	1.0 (0.9–1.0)	0.9 (0.9–1.0)	1.0 (0.9–1.1)	0.9 (0.8–1.1)
TAR, %	1.0 (1.0–1.1)	1.1 (1.0–1.1)	1.0 (0.9–1.1)	1.2 (0.9–1.5)
TBR, %	1.1 (0.9–1.4)	0.9 (0.8–1.1)	0.7 (0.5–1.1)	0.6 (0.3–1.2)
Mean glucose, mmol/L	0.8 (0.3–1.8)	2.3 (1.0–5.4)	1.8 (0.7–5.0)	2.1 (0.8–5.2)
AUCal, mmol/L	0.5 (0.1–2.0)	1.7 (0.5–6.4)	1.8 (0.4–8.6)	3.5 (0.5–25.7)
HbA1c, mmol/mol	1.1 (1.0–1.2)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	0.9 (0.8–1.1)

Note: Data are presented as OR with 95% CI. OR are adjusted for maternal age. pre-pregnancy body mass index and ethnicity. Statistically significant outcomes are displayed in bold characters ($p < .05$). Pre-eclampsia was not analysed because of only one event.

Abbreviations: AUCal, area under the curve above limit, which is AUC of glucose levels above 7.8 mmol/L; CI, confidence interval; glucose SD, standard deviation of the mean glucose concentrations; HbA1c, glycated haemoglobin; mean glucose, average glucose concentration calculated over the total period of time with CGM output; NICU, Neonatal Intensive Care Unit; OR, odds ratio; TAR, time spent above the upper limit of the glucose target range (>7.8 mmol/L) expressed as the percentage of the total period of time with CGM output; TBR, time spent below the lower limit of the glucose target range (<3.5 mmol/L) expressed as the percentage of the total period of time with CGM output; TIR, time spent in glucose target range of 3.5–7.8 mmol/L expressed as the percentage of the total period of time with available CGM output.

of the similarity in pathophysiology, given the need for insulin therapy in our patients with GDM.[15]

Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a $p \leq .05$.

IBM SPSS Statistics version 26 for Windows (IBM Corporation) was used for all analyses.

3 | RESULTS

The current study reports on 115 participants who were originally allocated to the CGM study arm of the GlucoMOMS trial, as depicted in the study outline in Figure 1. In the CGM group, the majority (71%) of eligible participants were of White European origin, whereas more than half of the non-eligible participants (because of insufficient CGM data for inclusion) were of other ethnicities (Table S1). No other differences between eligible and excluded participants were detected regarding demographics, type of diabetes, treatment and other characteristics.

3.1 | Baseline characteristics and glycaemic parameters

There were several differences between participants with type 1 diabetes (n = 50) and the composite group of participants with type 2 diabetes (n = 36) and insulin-treated GDM (n = 37) (Table 1). Participants with type 1 diabetes were younger and more often nulliparous and of White European origin. Participants with type 2 diabetes or gestational diabetes had a higher pre-pregnancy body mass index.

3.2 | Glycaemic parameters as pregnancy progressed

Table 2 displays the CGM metrics and HbA1c values over trimesters and per type of diabetes. For participants with type 1 diabetes, TIR increased as pregnancy progressed from a mean of 57% ± 15% in the first trimester to 66% ± 16% in the third trimester. TBR decreased as gestational age advanced; from 12% ± 10% in the first trimester to 7% ± 8% in the third trimester, and TAR remained stable across trimesters at a mean of 29% ± 18%. HbA1c increased slightly as pregnancy progressed, from 43 ± 4 mmol/mol to 46 ± 8 mmol/mol, although this difference did not achieve statistical significance.

In GDM, the TIR increased from 74% ± 13% in the second trimester to 78% ± 20% in the third trimester, compared with 63% ± 16% (in the first trimester) to 65% ± 14% (in the third trimester) for type 2 diabetes.

3.3 | Glycaemic metrics and pregnancy outcome

Higher mean glucose concentrations in the second trimester in pregnancies complicated by type 1 diabetes were associated with an increased risk of LGA (OR 2.6 [95% CI 1.1–6.2]). None of the other CGM metrics or HbA1c in either the first, second or third trimester were associated with neonatal hypoglycaemia, preterm birth or NICU admission (Table 3A). There was only one case of pre-eclampsia, which was insufficient to perform binary logistic regressions. In second trimester all CGM metrics were associated with z-score birth weight. In the third trimester only TBR seemed to have an association with z-score birth weight (OR −1.6 [95% CI −3. to −0.3]) (Table 4). In type 2 diabetes and insulin-treated GDM, the AUCal in the third trimester was associated with LGA (OR 10.0 [95% CI 1.4–72.8]). None of the other CGM metrics were associated with LGA in pregnancies complicated by type 2 diabetes or gestational diabetes, nor was HbA1c (OR 1.1 [95% CI

TABLE 4 Glycaemic variables and their relationship with birth weight z-scores

	DM 1 OR (95% CI)	DM 2/GDM OR (95% CI)
First trimester		
TIR, %	−0.61 (−1.65 to 0.43)	0.10 (−0.69 to 0.88)
TAR, %	0.65 (−0.13 to 1.42)	0.20 (−0.64 to 1.03)
TBR, %	−1.17 (−2.78 to 0.44)	−3.09 (−4.94 to 1.23)
Mean glucose, mmol/L	7.81 (−4.08 to 19.73)	8.53 (−7.82 to 24.88)
AUCal, mmol/L	11.23 (−13.34 to 35.80)	13.36 (−28.87 to 55.59)
HbA1c, mmol/mol	−0.39 (−1.99 to 1.21)	0.23 (−0.80 to 1.27)
Second trimester		
TIR, %	**−0.72 (−1.37 to −0.08)**	−0.46 (−1.07 to 0.14)
TAR, %	**0.78 (0.27–1.28)**	0.44 (−0.019 to 1.07)
TBR, %	**−1.69 (−2.97 to −0.40)**	0.54 (−1.56 to 2.63)
Mean glucose, mmol/L	**12.20 (4.66–19.73)**	3.52 (−7.84 to 14.88)
AUCal, mmol/L	**16.12 (1.93–30.3)**	23.23 (−3.95 to 50.41)
HbA1c, mmol/mol	0.33 (−0.73 to 1.39)	0.08 (−1.08 to 1.24)
Third trimester		
TIR, %	−0.23 (−0.94 to 0.49)	**−0.47 (−0.92 to − 0.01)**
TAR, %	0.43 (−0.15 to 1.02)	0.49 (−0.02 to 1.00)
TBR, %	**−1.64 (−3.01 to −0.27)**	0.65 (−0.99 to 2.29)
Mean glucose, mmol/L	7.16 (−1.72 to 16.04)	**8.45 (0.24–16.67)**
AUCal, mmol/L	6.87 (−11.71 to 25.44)	16.64 (−1.67 to 34.55)
HbA1c, mmol/mol	0.26 (−0.79 to 1.32)	0.73 (−0.34 to 1.80)

Abbreviations: AUCal, area under the curve above limit, which is AUC of glucose levels above 7.8 mmol/L; GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; NICU, neonatal Intensive Care Unit; TAR, time above target range; TBR, time below target range; TIR, time in range.

1.0–1.3]). Moreover, none of the CGM metrics or HbA1c were associated with other outcomes of interest, including pre-eclampsia, preterm birth and NICU admission in any of the diabetes types (Table 3B). In the third trimester, TIR and mean glucose showed an association with z-score birth weight [OR −0.5 (95% CI −0.9 to −0.01) and OR 8.5 (95% CI 0.2–16.7) respectively Table 4].

4 | DISCUSSION

In this post-hoc analysis of a randomized clinical trial on the utility of CGM in pregnancy, we found an association between glucose AUCal and LGA in type 2 diabetes and insulin-treated GDM, and an association with TIR and mean glucose for birth weight in z-scores, but no such associations with other CGM metrics, or other perinatal outcomes. Our findings can provide clinicians with guidance on the utility of CGM metrics in the management of type 2 diabetes and insulin-treated GDM pregnancies, as sensor technology has seen rapid uptake largely driven by the availability and consumer friendly nature compared with SMBG, rather than strong evidence.

In two secondary analyses of the CONCEPTT trial[4,5] an association between TIR and LGA, in both the second and the third trimester was found in women with type 1 diabetes. This is in contrast to our findings in pregnancies with type 1 diabetes, in which a higher mean glucose concentration showed a stronger association with LGA than TIR. Moreover, TIR was also associated with neonatal hypoglycaemia. Yamamoto et al. reported an association between TIR, TAR and HbA1c and neonatal hypoglycaemia.[6] The fact that the CONCEPTT trial used real-time CGM, whereas our sample used offline CGM may underlie these differences. The use of real-time CGM in the CONCEPTT trial probably gave women a full understanding of their glycaemic control. This may have led to a higher TIR, which might give

TABLE 3B Glycaemic variables and their relationship with pregnancy outcomes in women with type 2 diabetes and GDM (n = 73)

	Neonatal hypoglycaemia (n = 22) OR (95% CI)	Large for gestational age (n = 15) OR (95% CI)	Pre-eclampsia (n = 3) OR (95% CI)	Preterm birth (<37 weeks gestational age) (n = 12) OR (95% CI)	NICU admission (n = 2) OR (95% CI)
First trimester					
TIR, %	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.1)	0.9 (0.8–1.1)	-
TAR, %	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (1.0–1.1)	-
TBR, %	0.5 (0.1–2.4)	0.4 (0.0–3.7)	0.8 (0.3–2.2)	1.1 (0.8–1.4)	-
Mean glucose, mmol/L	13.6 (0.4–466)	10.4 (0.3–385)	6.3 (0.1–631)	1.1 (0.1–11.2)	-
AUCal, mmol/L	2.0 (0.1–30.6)	23.8 (0.7–747)	1.9 (0.1–60)	0.4 (0.2–7.2)	-
HbA1c, mmol/mol	1.1 (1.0–1.2)	1.0 (0.9–1.1)	1.0 (0.9–1.2)	1.0 (0.9–1.0)	-
Second trimester					
TIR, %	1.0 (1.0–1.1)	1.0 (0.9–1.1)	1.6 (0.7–3.7)	1.0 (0.9–1.1)	1.4 (0.7–3.3)
TAR, %	1.0 (0.9–1.0)	1.0 (0.9–1.1)	0.8 (0.4–1.3)	1.0 (1.0–1.1)	0.9 (0.6–1.4)
TBR, %	1.0 (0.8–1.2)	1.0 (0.7–1.4)	0.0 (0.0–0.0)	0.7 (0.6–1.0)	-
Mean glucose, mmol/L	0.4 (0.1–1.6)	1.4 (0.3–7.7)	1.0 (0.0–21.3)	4.5 (0.9–26.8)	-
AUCal, mmol/L	0.3 (0.0–4.8)	6.3 (0.9–45.3)	0.4 (0.0–5355)	1.0 (0.1–9.5)	-
HbA1c, mmol/mol	0.9 (0.8–1.1)	0.9 (0.7–1.1)	1.1 (0.8–1.6)	1.2 (1.0–1.4)	-
Third trimester					
TIR, %	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.0)	0.9 (0.7–1.2)
TAR, %	1.0 (1.0–1.1)	1.1 (1.0–1.1)	1.0 (0.9–1.2)	1.0 (1.0–1.1)	1.2 (0.7–2.1)
TBR, %	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.9 (0.5–1.4)	1.0 (0.8–1.2)	0.7 (0.2–2.8)
Mean glucose, mmol/L	1.4 (0.6–3.3)	2.6 (1.0–6.9)	6.3 (0.1–631)	0.8 (0.2–2.3)	-
AUCal, mmol/L	1.1 (0.3–4.3)	**10.0 (1.4–72.8)**	0.6 (0.0–28.8)	0.7 (0.1–5.2)	0.9 (0.2–49)
HbA1c, mmol/mol	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.7 (0.5–1.4)	1.0 (0.9–1.2)	-

Note: Data are presented as OR with 95% CI. ORs are adjusted for maternal age. pre-pregnancy body mass index and ethnicity. Statistically significant outcomes are displayed in bold characters ($p < .05$).

Abbreviations: AUCal, area under the curve above limit, which is AUC of glucose levels above 7.8 mmol/L; CI, confidence interval; glucose SD, standard deviation of the mean glucose concentrations; HbA1c, glycated haemoglobin; mean glucose, average glucose concentration calculated over the total period of time with CGM output; NICU, Neonatal Intensive Care Unit; OR, odds ratio; TAR, time spent above the upper limit of the glucose target range (>7.8 mmol/L) expressed as the percentage of the total period of time with CGM output; TBR, time spent below the lower limit of the glucose target range (<3.5 mmol/L) expressed as the percentage of the total period of time with CGM output; TIR, time spent in glucose target range of 3.5–7.8 mmol/L expressed as the percentage of the total period of time with available CGM output.

a better pregnancy outcome. In the GlucoMOMs trial the offline glucose profiles were obtained by clinicians retrospectively after each week of blinded CGM, insights were discussed with the patient and therapy was advised accordingly. As women did not have any real-time feedback, it is probable that awareness of factors beneficial to their own glycaemic control went unnoticed. This might be one of the reasons why we see less of a relationship between TIR and LGA in our study. This could be relevant for our findings in type 2 diabetes and GDM and investigating the utility of real-time CGM should be the focus of future studies in type 2 diabetes and GDM. Another key difference was the larger sample size (n = 157) of the CONCEPTT trial, with more statistical power.

Two studies have previously investigated the role of glucose sensors, one in women with type 2 diabetes and one in women with insulin-treated GDM. The FlashMom pilot study randomized women with pregestational diabetes to flash glucose monitoring (flash) and SMBG. In this study six women had type 2 diabetes, two of them were randomized to flash. There were no differences in perinatal outcomes.[16] In a retrospective cohort in 12 women with GDM and 53 with type 2 diabetes, Bitar et al. found that higher TIR (>70%) was associated with increased adverse neonatal and maternal outcomes. However, neither of these studies investigated the role of CGM metrics other than TIR on perinatal outcomes.[17]

To our knowledge, this is the first study to investigate, in a larger randomized group, the relation of a broad spectrum of CGM metrics with pregnancy outcomes in a group of insulin-treated type 2 diabetes and insulin-treated GDM pregnancies.

We acknowledge the limitations of this post-hoc analysis of the GlucoMOMS trial. The primary study was not powered to detect clinical differences between subgroups according to type of diabetes in the CGM group. To increase power, we decided to combine type 2 diabetes and insulin-treated GDM. Furthermore, some selective attrition affected our study: white European participants would probably stay in a trial and use the CGM as instructed.[18-20] This may have limited the external validity of our findings. Moreover, we were not able to extract the amount of full 5-day CGM cycles each subject had and could not distinguish between nocturnal and diurnal CGM metrics, as Law et al showed the nocturnal metrics to be off larger significance than the diurnal metrics.[21] Lastly, the incidence of pre-eclampsia in our cohort was low at only 4%, which is an incidence of pre-eclampsia comparable with pregnancies without diabetes. The incidence of pre-eclampsia for pregnancies with diabetes is generally reported to be markedly higher, complicating about 10% of pregnancies with diabetes.[22] This low incidence of pre-eclampsia decreased the power to detect a potential association between CGM metrics and pre-eclampsia in type 1 diabetes in this study. The original GlucoMOMS trial found a lower (non-significantly different) incidence of pre-eclampsia in the CGM group (4%) compared with participants who received standard care (12%), a difference attributed to chance.[10] Lastly, a caveat in clinical application is that our study was observational in design, which precludes any firm statements on the benefit women with type 2 diabetes and insulin-treated GDM may derive from CGM-derived AUCal guided treatment.

Given the rapid uptake of sensor technology among type 2 diabetes and GDM in high income countries, adequately powered studies on the utility of sensor output in guiding insulin treatment with the aim of optimizing pregnancy outcomes may also contribute to advanced technologies and treatment for diabetes recommendations for CGM targets in type 2 diabetes and GDM pregnancies, which are currently based on consensus and only scarce evidence.[9,23]

When merely focusing on TIR or TAR, an incomplete view of glucose regulation and exposure to hyperglycaemia is obtained. AUCal complements these metrics. However, TIR is an intuitive parameter providing patients with more insight into the quality of their glycaemic control, as compared with abstract metrics such as HbA1c and AUCal, if added to the device interface. Considering patient-centred care, including adequate education for self-management, TIR therefore is a valuable asset.

In conclusion, CGM metrics in both type 1 diabetes and type 2 diabetes or insulin-treated GDM might be possible determinants of LGA. The novelty of this study is that CGM metrics in type 2 diabetes or insulin-treated GDM may be able to indicate LGA.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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