ORIGINAL ARTICLE

Continuous glucose monitoring parameters in pregnancy-related complications in patients with type 1 diabetes: a retrospective cohort study

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KEY WORDS

continuous glucose monitoring, glycemic variability, neonatal complications, pregnancy, type 1 diabetes

ABSTRACT

INTRODUCTION Continuous glucose monitoring (CGM) improves pregnancy outcomes in patients with type 1 diabetes (T1D).

OBJECTIVES The primary study objective was to analyze associations between numerous novel CGM parameters and neonatal complications, such as large-for-gestational-age (LGA) neonates, hypoglycemia, hyperbilirubinemia, transient breathing disorders, preterm births, as well as pre-eclampsia.

PATIENTS AND METHODS In this single-center retrospective cohort study, we recruited 102 eligible pregnant women with T1D who were treated with sensor-augmented pumps with suspend-before-low function from the first trimester. The pregnant patients were admitted for at least 1 control hospital visit in each trimester of gestation for anthropometric and laboratory measurements and collection of sensor data.

RESULTS The median (interquartile range) percentage values for glycated hemoglobin (HbA_{1c}) (first trimester, 6.23 [5.91–6.9]; second trimester, 5.49 [5.16–5.9]; third trimester, 5.75 [5.39–6.29]) and for time-in-range (first trimester, 72.4 [67.3–80.3]; second trimester, 72.5 [64.7–79.6]; third trimester, 75.9 [67.1–81.4] met the criteria of well-controlled T1D in each trimester of pregnancy. Nonetheless, we noted 27% of LGA births, 25% of neonatal hypoglycemia, 33% of hyperbilirubinemia, and 13% of preterm births. Worse glycemic control and more glycemic fluctuations in the second and third trimesters were mainly associated with increased risk of LGA at birth, transient breathing disorders, and hyperbilirubinemia.

CONCLUSIONS CGM parameters (mean of daily differences, high blood glucose index, glycemic risk assessment in diabetes equation, or continuous overall net glycemic action) in the patients with T1D are significantly associated with the increased risk of LGA at birth and neonatal transient breathing disorders and hyperbilirubinemia. However, we did not find evidence that novel CGM indices could be more effective in predicting those events than the commonly used CGM parameters or HbA_{1c} levels.

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INTRODUCTION According to the current guidelines based on the outcomes of the CONCEPTT (Continuous glucose monitoring in pregnant women with type 1 diabetes) randomized trial, continuous glucose monitoring (CGM) devices are recommended in standard clinical care protocols in pregnant women with type 1 diabetes (T1D).[1,2] The use of CGM systems is linked with improvement in long-term glycemic control defined by glycated hemoglobin (HbA_{1c}) levels. It was also associated with reduced fear of hypoglycemia and the risk of large-for-gestational-age

WHAT'S NEW?

Our study shed new light on the role of continuous glucose monitoring (CGM) glycemic metrics as potential predictors of various perinatal complications in pregnant women with type 1 diabetes. In our well-powered analysis, we revealed that numerous parameters of short- and long-term glycemic control are significantly associated with the risk of adverse pregnancy outcomes, such as large-for-gestational-age births and neonatal transient breathing disorders and hyperbilirubinemia. The fact that we recruited the largest number of participants treated with insulin pumps and CGM devices, as compared with other large trials, is the study's greatest strength.

(LGA) births, length of hospital stay, and neonatal hypoglycemia.[2-4]

Further observations demonstrated that several glycemic indices, such as mean glucose values, SD of mean sensor glucose values, or time spent in the target range (TIR) are significantly associated with the risk of LGA births, pre-eclampsia, preterm births, neonatal hypoglycemia, or admission to neonatal intensive care units.[5,6] The findings presented in our most recent publications support the opinion that worse glycemic control manifested in differences in novel glycemic control metric values is linked with increased risk of LGA at birth.[7,8]

According to the current recommendations, pregnant patients with T1D should spend more than 70% of their daily time in the target glucose range of 63–140 mg/dl (3.5–7.8 mmol/l) throughout the pregnancy. The target HbA_{1c} level for the first trimester is below 6.5% (47.5 mmol/mol), and no higher than 6% (42.1 mmol/mol) in the second and third trimester.[9,10]

The primary study objective was to analyze potential associations between CGM parameters and the following gestational complications: LGA, neonatal hypoglycemia, hyperbilirubinemia, and transient breathing disorders, preterm births, and pre-eclampsia in both univariable and adjusted regression models. Our study introduces a range of novel parameters of glycemic variability, such as the mean of daily differences (MODD), mean amplitude of glycemic excursions (MAGE), and glycemic risk assessment in diabetes equation (GRADE). We hypothesized that those parameters could be more accurate in predicting the risk of pregnancy-related adverse outcomes, as compared with commonly used CGM metrics and HbA_{1c} levels. The secondary aim of the study was to analyze the differences in the long-term glycemic control (defined by the following CGM indices: TIR, time above range [TAR], time below range [TBR], mean glucose levels, and HbA_{1c} values) in the consecutive trimesters of pregnancy in patients who developed pregnancy-related complications and in the women with T1D who did not present those perinatal conditions.

PATIENTS AND METHODS

Study design and patient recruitment We conducted a single-center retrospective cohort study. All the participants included in the study cohort were recruited retrospectively from the registry of planned first-trimester hospital visits scheduled between 2017 and 2021 in the Department of Reproduction, Poznan University of Medical Sciences, Poznań, Poland. The patients were referred to our tertiary referral clinic as early as their pregnancy was confirmed. We selected women aged 18–45 years, with a documented history of T1D for at least 12 months at enrolment, who started a therapy with sensor-augmented pumps with suspend-before-low function in the first trimester of pregnancy in our clinic. The recruited patients were at 13 weeks' 6 days' gestation or less at baseline. We excluded patients with multiple pregnancies or women with early (first trimester) pregnancy loss or stillbirth. The age and type of pregnancy (singleton vs multiple) were verified with ultrasonography at the first visit in the clinic.

The Poznan University of Medical Sciences Bioethical Commission does not require an informed consent from the patients analyzed in retrospective studies and approves publication of the results of such studies.

Study procedures and applied devices Our standard clinical protocol for patients with T1D in a noncomplicated singleton pregnancy includes at least 3 short routine control hospital stays (up to 3–4 days) in the maternity unit throughout gestation. The first visit is scheduled at 13 weeks' and 6 days' gestation or earlier, the second between 20th and 24th week of pregnancy, and the last one between 33rd and 39th week of pregnancy. We admit the patients for more frequent visits if it is justified. In addition to those admissions, the patients are under routine control and have contact (at least every 2 weeks) with obstetricians and diabetologists to adapt the insulin dosage to individual requirements.

At the first control visit, all patients with T1D complete a medical questionnaire about their demographic status and medical history. Those self-reported data were used to analyze the baseline cohort characteristics in our study.

We educated every pregnant patient about insulin pump therapy at the first scheduled visit in our department. Every woman was equipped with a sensor-augmented insulin pump to use it continuously during the pregnancy (Medtronic MiniMed 640G insulin pump, Medtronic Guardian Link 3 transmitter, and Guardian Sensor 3; Medtronic, Northridge, California, United States). The devices were donated by the charity foundation "The Great Orchestra of Christmas Charity" (en.wosp.org.pl). Furthermore, every patient was individually educated about diet and carbohydrate counting,[11] glycemic goals, self-monitoring of blood glucose, and self-adjusting of insulin dose. We encouraged our patients to control their capillary glucose levels at random time points throughout the day. All women from our study cohort used the pumps with an activated predictive

low-glucose management to prevent episodes of hypoglycemia. Based on the current international and Polish recommendations, we informed the patients about their target glucose sensor and HbA_{1c} levels.[9,10]

Continuous glucose monitoring sensors and data processing methods The study participants underwent routine follow-up on each visit, and all data from the pumps and sensors were collected and uploaded into the CareLinkTM Clinical data management software (Medtronic, Northridge, California, United States). We downloaded the raw data in CSV format and organized it to calculate the parameters of glycemic control specific for each trimester of pregnancy. We assigned the data collected until the 13 weeks and 6 days, between 14 and 27 weeks and 6 days, and from 28 weeks of pregnancy to the first, second, and third trimester of pregnancy, respectively. We analyzed the data using the web application GlyCulator version 2.0.[12]

We used the application to calculate the following CGM parameters of glycemic control: mean glucose levels, TIR (63–140 mg/dl [3.5–7.8 mmol/l]), TAR (>140 mg/dl [>7.8 mmol/l]), TBR (<63 mg/dl [<3.5 mmol/l] and <54 mg/dl [<3.0 mmol/l]), coefficient of variation (%CV), glucose management indicator (GMI), area under the glycemic curve (AUC), M100, J-index, MODD, low blood glucose index (LBGI), high blood glucose index (HBGI), GRADE, GRADE attributed to hypo-, hyper-, and euglycemia, MAGE, and continuous overall net glycemic action (CONGA) 1–6 h interval. Average daily risk range (ADRR) was calculated using "iglu" package in R statistical software version 4.2.2. (R Foundation for Statistical Computing, Vienna, Austria).

Maternal and neonatal outcomes We assessed the following maternal outcomes in our study cohort: gestational weight gain, mode of delivery, pre-eclampsia, and HbA_{1c} and triglycerides levels. Gestational weight gain was defined as a difference between the patient's self-reported pregestational weight and the weight measured by the nurse at the last visit just before delivery. We defined pre-eclampsia as a newly diagnosed (after 20 weeks of gestation) systolic blood pressure equal to or above 140 mm Hg or diastolic blood pressure equal to or above 90 mm Hg associated with at least 1 of the following complications: proteinuria, increased creatinine and transaminase levels, neurologic and hematologic complications, fetal growth restriction, and placental insufficiency. We diagnosed pre-eclampsia in the patients with chronic hypertension only when their systolic blood pressure exceeded 140 mm Hg or diastolic blood pressure was greater than 90 mm Hg, and 1 of the complications mentioned above coexisted with elevated blood pressure values.[13]

The analyzed neonatal outcomes included: gestational age, preterm delivery (<37th gestational week), birth weight, macrosomia (birth weight >4000 g), LGA births (birth weight >90th centile), small-for-gestational-age births (birth weight <10th centile), placental weight, arterial umbilical pH value, neonatal hypoglycemia, transient breathing disorders, and hyperbilirubinemia. We calculated the birth weight centiles using the bulk percentile calculator (GROW v.8.0.6.1, Gestation Network, www.gestation.net).[14] The calculator adjusts the birth weight percentiles for maternal ethnicity, weight, height, parity, and the infant's sex and gestational age. We diagnosed neonatal hypoglycemia when neonatal blood glucose concentration was below 40 mg/dl (2.2 mmol/l) in a single laboratory measurement at least 3 hours after birth, in the first 24 hours of life. Neonatal hyperbilirubinemia was defined as clinically relevant jaundice that required phototherapy. Transient breathing disorders included transient tachypnea of the newborn and other relatively mild conditions that did not require intubation.

Laboratory measurements We determined the HbA_{1c} values in whole blood using the turbidimetric inhibition immunoassay, Tina-quant HbA_{1c} II test in a Cobas c311 analyzer (Roche Diagnostics, Rotkreuz, Switzerland). We determined the HbA_{1c} values in each trimester of pregnancy; the first measurement was performed in the first trimester (at baseline), the second between 20th and 24th gestational week, and the last one maximum 7 days before delivery. If HbA_{1c} values were measured twice in the same trimester, we used the average value. All laboratory measurements were performed at the certified central laboratory of the Obstetrics and Gynecology University Hospital in Poznań.

Statistical analysis We performed all statistical analyses using the Statistica software, version 13.3 (TIBCO Software, Palo Alto, California, United States), with installed Medical Bundle, version 4.0.67 (StatSoft Polska Sp. z o.o., Kraków, Poland). The Shapiro–Wilk test was used for testing the normality of data distribution. The potential differences between groups of normally distributed variables were tested using the parametric *t* test. We analyzed the non-normally distributed data using the nonparametric Mann–Whitney test. We used the univariable and multivariable logistic regression models to investigate the relationships between a dependent variable and several explanatory parameters. We considered *P* values to be significant if *P* was below 0.05.

We performed the following sample size calculations. To achieve 80% power at a 2-sided 5% significance level, we planned to include at least 74 (37 per arm) individuals in the study cohort to detect a between-group difference in TIR of 6% with SD of 9% in the analysis of differences between LGA and non-LGA subgroups. Based on the results of our previous work, we assumed the prevalence of LGA at about 30% to 40% in the whole study cohort.[7] To achieve

TABLE 1 Baseline demographic and clinical characteristics of the study cohort (n = 102)

Parameter		Value
Maternal age, y		30.7 (5.1)
Caucasian race, n (%)		102 (100)
Duration of diabetes, y		15 (8–20)
Age at diagnosis of diabetes, y		15 (10–24)
Gestational age at baseline, weeks		9 (7–11)
Primiparous, n (%)		54 (52.9)
Planning the pregnancy, n (%)		21 (20.6)
Body weight, kg		65.9 (60.5–79.4)
BMI, kg/m^2	Prepregnancy	23.5 (21.3–26.9)
	First trimester (baseline)	23.8 (21.8–27.9)
Prepregnancy BMI, n (%)	Overweight (25–30 kg/m^2)	29 (28.4)
	Obese (>30 kg/m^2)	10 (9.8)
HbA_{1c} at baseline	%	6.23 (5.91–6.9)
	mmol/mol	44.6 (41.1–51.9)
HbA_{1c} at baseline >6.5%, n (%)		39 (38.2)
Diabetes complications at baseline, n (%)	Diabetic retinopathy	12 (11.8)
	Diabetic nephropathy	12 (11.8)
White's classification, n (%)	B	26 (25.5)
	C	27 (26.5)
	D	31 (30.4)
	R	6 (5.9)
	F	6 (5.9)
	R/F	6 (5.9)
Insulin pump type, n (%)	Medtronic MiniMed 640G with smart guard technology	102 (100)

Data are presented as mean (SD) or median and interquartile range unless indicated otherwise.

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin

sufficient statistical power in univariable logistic regression models we had to recruit at least 100 patients.

RESULTS We recruited a group of 102 eligible pregnant women with T1D who were treated with sensor-augmented pumps with suspend-before-low technology. The baseline demographic and clinical characteristics of the study cohort are shown in TABLE 1. Our study cohort was ethnically homogenous. The mean (SD) age of the pregnant women was 30.7 (5.1) years. The median maternal pre-pregnancy BMI was 23.5 (21.3–26.9) kg/m^2. Only 21 pregnancies (20.5%) were planned. However, the median baseline HbA_{1c} was lower than 6.5% (ie, 6.23%), and the median TIR exceeded 72%. The pump therapy was initiated at the first admission at 9 (7–11) weeks of pregnancy. The median (interquartile range [IQR]) time of the sensor use was 29.5 (22.9–46), 76.6 (46.7–91.1), and 50.3 (34.5–64) days in the first, second, and third trimester, respectively. Finally, the median (IQR) time of the sensor use in the second and third trimester was 75.6% (49.6%–86.9%). The majority of the patients were primiparous and did not present diabetes complications.

Maternal outcomes are provided in TABLE 2. The mean and median HbA_{1c}, TIR, and TAR values met the criteria of well-controlled T1D in each trimester of pregnancy. The incidence of LGA births and neonatal hyperbilirubinemia requiring phototherapy in the whole study group was close to 30% (TABLE 3).

The primary study objective was to analyze the potential associations between the multiple CGM metrics and the risk of several gestational complications. The univariable and multivariable logistic regression models adjusted for maternal age, pregestational BMI, gestational weight gain, and duration of diabetes revealed that multiple second- and third-trimester glycemic indices rather than the first-trimester parameters were significantly associated with the LGA risk (TABLE 4, Supplementary material, *Table S1*). Due to the inadequate study sample size, the results of multivariable regression are shown in Supplementary material. Only 2 first-trimester glycemic metrics, MODD and CONGA 1 h, were positively associated with the risk of neonatal hypoglycemia. The risk of neonatal hyperbilirubinemia was associated with multiple second- and third-trimester indices, such as TIR, TAR, MAGE, MODD, HBGI, M100, J-index,

TABLE 2 Maternal outcomes in the whole study cohort (n = 102)

Maternal outcomes		First trimester	Second trimester	Third trimester
BMI, kg/m^2		23.8 (21.8–27.9)	25.5 (23.3–29.3)	28.3 (25.9–31.5)
Body weight, kg		65.9 (60.5–79.4)	71.2 (65–82.5)	78 (70.9–89)
Gestational weight gain, kg			12.9 (5.5)	
Pre-eclampsia, n (%)			10 (9.8)	
Cesarean section, n (%)			72 (70.6)	
HbA_{1c}	%	6.23 (5.91–6.9)	5.49 (5.16–5.9)	5.75 (5.39–6.29)
	mmol/mol	44.6 (41.1–51.9)	36.5 (32.9–41)	39.3 (35.4–45.2)
Triglycerides, mg/dl		63.9 (48.4–83.7)	126.4 (102.6–160.3)	240.7 (196.3–292.9)
Sensor time, d		29.5 (22.9–46)	76.6 (46.7–91.1)	50.3 (34.5–64)
Sensor mean glucose levels	mg/dl	113.4 (104.8–121)	115.4 (105.3–124.1)	114.2 (106.3–125.4)
	mmol/l	6.30 (5.82–6.72)	6.41 (5.85–6.89)	6.34 (5.91–6.97)
TAR 140 mg/dl, %		21.7 (14.2–27.4)	22.4 (13.2–30.9)	20.4 (13.7–30.1)
TIR 63–140 mg/dl, %		72.4 (67.3–80.3)	72.5 (64.7–79.6)	75.9 (67.1–81.4)
TBR 63 mg/dl, %		4.5 (2.7–7.9)	4.2 (2–7.4)	2.6 (1–4.6)
TBR 54 mg/dl, %		1.5 (0.5–2.9)	1.5 (0.5–2.8)	0.6 (0.2–1.4)
Spent more than 70% of time in TIR, n (%)		61 (59.8)	60 (58.8)	66 (64.7)
%CV		33.3 (29.6–36.6)	31.9 (28.1–35.3)	29.8 (25.8–32.4)
AUC		113.4 (104.8–120.9)	115.4 (105.3–124.1)	114.2 (106.3–125.4)
AUC over 140 mg/dl		5.93 (3.35–9.76)	6.38 (2.95–10.53)	5.24 (2.7–10.22)
Glucose management indicator, %		5.57 (5.27–5.83)	5.64 (5.28–5.94)	5.59 (5.32–5.99)
MODD, mg/dl		37.8 (30.3–43)	36.5 (31.1–42.7)	32.3 (29–38.1)
LBGI		2.29 (1.62–3.12)	2.20 (1.48–3.08)	1.57 (1.05–2.5)
HBGI		1.41 (0.84–2.16)	1.54 (0.76–2.4)	1.3 (0.74–2.29)
ADRR		33.09 (8.22)	31.25 (7.42)	26.21 (7.13)
GRADE		3.97 (3.24–4.81)	3.98 (3.1–4.79)	3.54 (2.84–4.66)
GRADE hypo, %		20.3 (12.7–38.3)	21.4 (11.2–34.2)	12.4 (6–26.5)
GRADE eu, %		21.1 (16.5–27.7)	22.9 (17.9–27.2)	26.5 (20.9–34.1)
GRADE hyper, %		54.2 (38.2–64)	53.1 (37.3–64.4)	54.9 (41–69.1)
MAGE, mg/dl		97.4 (84.7–110.2)	96.7 (84.7–108.5)	87.3 (79–102)
M100		121.9 (106.8–136)	120.7 (107.3–133.1)	113.3 (97.6–131.2)
J-index		22.9 (19.3–26.4)	23.4 (18.7–27.7)	22 (18.6–27.2)
CONGA 1 h		24.4 (21.6–28)	22.1 (20.4–25.7)	19.5 (18–22.1)
CONGA 2 h		31 (26.9–34.9)	29.4 (26–33.3)	26.3 (23.3–29.1)
CONGA 3 h		33.2 (28.1–36.8)	31.7 (27.6–35.8)	28.3 (25.2–32.3)
CONGA 4 h		33.5 (28.7–38)	32.4 (27.5–36.8)	29.1 (26.1–33.4)
CONGA 6 h		32.1 (28–37.4)	32.6 (27.8–36.5)	28.9 (25.8–34)

Data are presented as mean (SD) or median and interquartile range unless indicated otherwise.

SI conversion factors: to convert glucose to mmol/l, multiply by 0.0555; triglycerides to mmol/l, by 0.0113.

Abbreviations: %CV, coefficient of variation; ADRR, average daily risk range; AUC, area under the glycemic curve; CONGA, continuous overall net glycemic action; GRADE, glycemic risk assessment in diabetes equation; GRADE eu, GRADE attributed to euglycemia; GRADE hypo, GRADE attributed to hypoglycemia; GRADE hyper, GRADE attributed to hyperglycemia; HBGI, high blood glucose index; LBGI, low blood glucose index; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; TAR, time above range; TBR, time below range; TIR; time in range; others, see **TABLE 1**

and CONGA 1–6 h. In both univariable and multivariable regression analyses, several second-trimester parameters were significantly associated with the risk of transient breathing disorders in the newborn (**TABLE 4**). The regression analysis revealed that the risk of preterm birth was mainly associated with the first-trimester parameters reflecting the levels of glucose control and glycemic variability. Finally, multiple glycemic control parameters were found to be related to the risk of pre-eclampsia in univariable regression models in each trimester. However, none of them remained significantly associated with this complication after adjustment for confounders (**TABLE 4**).

The secondary analysis of the study data revealed that mothers of LGA infants presented markedly higher HbA_{1c} levels in the second and third trimester of pregnancy. Furthermore,

TABLE 3 Neonatal outcomes in the whole study cohort (n = 102)

Neonatal outcomes		Value
Gestational age, d		268 (264–270)
Preterm births, n (%)	Preterm <37 weeks	13 (12.7)
	Early preterm <34 weeks	3 (2.9)
Neonatal birth weight, g		3496 (611)
Large-for-gestational-age >90th centile, n (%)		28 (27.5)
Macrosomia >4000 g, n (%)		18 (17.6)
Small-for-gestational-age <10th centile, n (%)		11 (10.8)
Placental weight, g		610 (520–740)
Umbilical artery pH value		7.27 (7.23–7.3)
Umbilical artery pH <7.0, n (%)		2 (2)
Umbilical vein pH value		7.31 (7.27–7.34)
Other neonatal complications, n (%)	Transient breathing disorders	19 (18.6)
	Hypoglycemia <40 mg/dl[a]	25 (24.5)
	Hyperbilirubinemia[b]	34 (33.3)

Data are presented as mean (SD) or median and interquartile range unless indicated otherwise.

a Plasma glucose concentrations <40 mg/dl (2.2 mmol/l) in a single laboratory measurement performed at least 3 hours after birth, in the first 24 hours of life

b Clinically relevant neonatal jaundice that required phototherapy

the mothers of LGA infants had higher second- and third-trimester mean glucose levels and spent more time above the target glucose values in late pregnancy (TABLE 5).

There were no differences throughout gestation in HbA_{1c} values and CGM glycemic control indices between the mothers of infants with hypoglycemia and the mothers of euglycemic neonates. However, we detected significantly lower triglyceride levels in the first trimester of pregnancy in the mothers of infants with neonatal hypoglycemia (Supplementary material, *Table S2*). The tables presenting less significant data are shown in Supplementary material. The mothers of newborns with hyperbilirubinemia requiring phototherapy demonstrated significantly worsened second- and third-trimester glycemic control parameters (TIR, TAR, mean glucose values) as compared with the mothers of newborns without this condition. No other parameters were significantly changed (TABLE 6).

The mothers of neonates with transient breathing disorders presented significantly increased second-trimester HbA_{1c} levels in comparison with the mothers of neonates without breathing disorders (Supplementary material, *Table S3*). We also found changes in the first-trimester TIR and TAR values in the patients with preterm births, and in HbA_{1c} values in each trimester of pregnancy in the women diagnosed with pre-eclampsia, as compared with the patients not affected by these conditions (TABLES 7 and 8).

DISCUSSION The primary study objective was to investigate potential associations between various CGM metrics and perinatal complications. In our well-powered analysis, we revealed that numerous parameters of short- and long-term glycemic control could be useful in the prediction of those events. Slightly worse glycemic outcomes in the second and third trimester were mainly associated with the increased risk of adverse pregnancy outcomes in our study cohort, as compared with glycemic outcomes in early pregnancy.

Most of the patients from our study group achieved optimal glycemic control, defined as the mean HbA_{1c} levels equal to or below 6.5% in early pregnancy, and equal to or below 6% in the following trimesters, as well as mean TIR values equal to or above 70% in each trimester of gestation. Our patients achieved better glycemic control defined by TIR values than women in other studies conducted in the western populations, in which mean TIR values ranged from around 50% to around 68% throughout gestation.[2,5,15-17] We believe that the better glycemic outcomes noted in our study cohort may be associated with our intensive management protocol, which includes at least 1 short hospitalization in each trimester of pregnancy and regular short contacts (at least every 2 weeks) with obstetricians and diabetologists. Contrary to the mentioned reports[2,5,15-17], Ling et al[18] noted even higher TIR values in their study cohort.

Achieving optimal glycemic control may be insufficient to limit high incidence of adverse pregnancy outcomes in pregnant women with T1D. Despite achieving expected glycemic results, around 30% of pregnancies in our study group were complicated by LGA birth. In our recent conference paper,[19] we proposed that the introduction of even more strict glycemic targets should be considered to restrict the risk of LGA births in patients with T1D. The incidence of LGA births in the previous studies was dramatically higher as compared with our results, and even exceeded 50%.[2,3,5,16,20-24] Our findings can be directly

TABLE 4 Associations between continuous glucose monitoring parameters and adverse perinatal outcomes, univariable models (n = 102) (continued on the next page)

Parameter	LGA	Hypoglycemia	Hyperbilirubinemia	Transient breathing disorders	Preterm birth	Pre-eclampsia
First trimester						
Mean glucose	1.03 (0.99–1.08)	1.01 (0.97–1.06)	1.01 (0.97–1.05)	1.03 (0.98–1.07)	1.07 (1.01–1.14)[a]	1.04 (0.98–1.11)
TAR	1.05 (1–1.1)	1.02 (0.97–1.07)	1.02 (0.97–1.06)	1.05 (0.99–1.1)	1.1 (1.02–1.18)[a]	1.05 (0.98–1.13)
TIR	0.96 (0.91–1.01)	0.98 (0.93–1.04)	0.98 (0.94–1.03)	0.95 (0.89–1.01)	0.88 (0.81–0.96)[a]	0.95 (0.87–1.02)
AUC	1.03 (0.99–1.07)	1.01 (0.97–1.06)	1.01 (0.97–1.05)	1.03 (0.98–1.07)	1.07 (1.01–1.14)[a]	1.04 (0.98–1.11)
AUC over 140 mg/dl	1.04 (0.96–1.13)	1.03 (0.95–1.13)	1.03 (0.95–1.12)	1.03 (0.94–1.13)	1.15 (1.02–1.13)[a]	1.09 (0.98–1.21)
HbA_{1c}	1.47 (0.85–2.54)	1 (0.57–1.77)	0.8 (0.47–1.38)	1.38 (0.76–2.54)	0.81 (0.37–1.75)	2.28 (1.06–4.89)[a]
GMI	2.51 (0.76–8.27)	1.47 (0.44–4.92)	1.42 (0.47–4.32)	2 (0.55–7.32)	7.05 (1.33–37.23)[a]	3.22 (0.57–18.1)
%CV	1.01 (0.93–1.11)	1.06 (0.97–1.16)	1.04 (0.96–1.14)	1.01 (0.91–1.11)	1.15 (1.02–1.29)[a]	1.11 (0.98–1.25)
MAGE	1.02 (0.99–1.04)	1.02 (0.99–1.04)	1.01 (0.99–1.03)	1.01 (0.98–1.03)	1.04 (1.01–1.07)[a]	1.04 (1.001–1.07)[a]
MODD	1.04 (0.99–1.1)	1.05 (0.99–1.11)	1.01 (0.96–1.06)	1.05 (0.99–1.11)	1.05 (0.99–1.12)	1.06 (0.99–1.14)
LBGI	0.78 (0.5–1.21)	0.99 (0.65–1.52)	0.98 (0.66–1.44)	0.95 (0.61–1.51)	1 (0.6–1.69)	0.88 (0.46–1.66)
HBGI	1.23 (0.82–1.84)	1.17 (0.77–1.77)	1.14 (0.77–1.69)	1.17 (0.76–1.8)	2.01 (1.12–3.6)[a]	1.48 (0.89–2.43)
ADRR	1.04 (0.98–1.11)	1.05 (0.98–1.12)	1.04 (0.98–1.1)	1.01 (0.95–1.08)	1.06 (0.98–1.16)	1.09 (0.98–1.2)
M100	1.01 (0.99–1.04)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.02 (0.99–1.04)	1.05 (1.02–1.09)[a]	1.03 (0.99–1.06)
J-index	1.04 (0.97–1.13)	1.03 (0.96–1.12)	1.03 (0.95–1.1)	1.03 (0.95–1.12)	1.14 (1.02–1.28)[a]	1.08 (0.98–1.19)
CONGA 1 h	1.15 (1.01–1.3)[a]	1.16 (1.01–1.33)[a]	1.15 (1.02–1.3)[a]	1.11 (0.97–1.27)	1.17 (1–1.38)	1.17 (0.97–1.4)
CONGA 2 h	1.07 (0.98–1.17)	1.09 (0.99–1.2)	1.08 (0.99–1.17)	1.04 (0.95–1.15)	1.14 (1.01–1.28)[a]	1.16 (1.01–1.34)[a]
CONGA 3 h	1.04 (0.97–1.12)	1.06 (0.98–1.15)	1.04 (0.97–1.12)	1.03 (0.95–1.11)	1.11 (1.004–1.22)[a]	1.12 (1–1.25)
CONGA 4 h	1.03 (0.96–1.1)	1.05 (0.98–1.13)	1.03 (0.97–1.1)	1.01 (0.94–1.09)	1.09 (1.001–1.2)[a]	1.1 (0.99–1.21)
CONGA 6 h	1.02 (0.96–1.09)	1.05 (0.98–1.13)	1.03 (0.97–1.09)	1.02 (0.95–1.09)	1.1 (1.01–1.2)[a]	1.11 (1.01–1.22)[a]
GRADE	1.24 (0.83–1.84)	1.21 (0.8–1.83)	1.17 (0.8–1.72)	1.36 (0.88–2.11)	2.57 (1.39–4.75)[a]	1.47 (0.84–2.6)
GRADE eu	0.98 (0.92–1.03)	0.99 (0.93–1.05)	0.99 (0.94–1.04)	0.98 (0.92–1.04)	0.88 (0.78–0.98)[a]	0.94 (0.86–1.04)
GRADE hypo	0.98 (0.95–1.01)	0.99 (0.96–1.02)	0.99 (0.97–1.02)	0.99 (0.96–1.02)	0.99 (0.95–1.03)	0.98 (0.94–1.03)
GRADE hyper	1.03 (1–1.06)	1.01 (0.98–1.04)	1.01 (0.98–1.04)	1.01 (0.98–1.05)	1.04 (1–1.09)	1.03 (0.99–1.09)
Second trimester						
Mean glucose	1.05 (1.01–1.08)[a]	1.02 (0.98–1.05)	1.04 (1.01–1.08)[a]	1.03 (1–1.08)	1.04 (0.99–1.08)	1.05 (1–1.11)
TAR	1.05 (1.01–1.09)[a]	1.02 (0.98–1.06)	1.05 (1.01–1.09)[a]	1.04 (0.99–1.08)	1.04 (0.99–1.09)	1.06 (1–1.12)
TIR	0.95 (0.91–0.99)[a]	0.98 (0.94–1.03)	0.96 (0.92–0.99)[a]	0.96 (0.91–1.01)	0.96 (0.91–1.02)	0.95 (0.88–1.01)
AUC	1.05 (1.01–1.08)[a]	1.02 (0.98–1.05)	1.04 (1.01–1.08)[a]	1.03 (1–1.08)	1.04 (0.99–1.08)	1.05 (1–1.11)
AUC over 140 mg/dl	1.09 (1.002–1.19)[a]	1.05 (0.96–1.14)	1.11 (1.02–1.2)[a]	1.1 (1.003–1.21)[a]	1.08 (0.98–1.2)	1.13 (1.004–1.27)[a]
HbA_{1c}	2.05 (0.97–4.31)	0.89 (0.41–1.9)	1.33 (0.68–2.62)	3.27 (1.33–8.06)[a]	2.5 (1.01–6.2)[a]	5.93 (1.69–20.78)[a]
GMI	3.47 (1.24–9.70)[a]	1.68 (0.62–4.5)	2.99 (1.15–7.78)[a]	2.63 (0.86–8.05)	2.74 (0.77–9.75)	4.5 (0.97–20.79)
%CV	1.03 (0.94–1.13)	1.06 (0.96–1.17)	1.06 (0.97–1.15)	1.09 (0.98–1.22)	1.07 (0.95–1.21)	1.1 (0.95–1.27)
MAGE	1.02 (1–1.05)	1.01 (0.99–1.04)	1.03 (1.001–1.05)[a]	1.03 (1–1.06)	1.02 (0.99–1.06)	1.04 (1–1.08)
MODD	1.05 (0.99–1.11)	1.05 (0.99–1.11)	1.04 (0.99–1.1)	1.06 (1–1.13)	1.05 (0.98–1.13)	1.07 (0.98–1.16)
LBGI	0.64 (0.41–0.99)[a]	0.88 (0.59–1.29)	0.74 (0.51–1.08)	0.86 (0.55–1.33)	0.74 (0.43–1.27)	0.6 (0.3–1.21)
HBGI	1.54 (1.02–2.34)[a]	1.27 (0.84–1.91)	1.63 (1.09–2.45)[a]	1.6 (1.02–2.51)[a]	1.46 (0.89–2.40)	1.8 (1.02–3.17)[a]
ADRR	1.03 (0.97–1.09)	1.05 (0.98–1.12)	1.03 (0.98–1.1)	1.07 (1–1.15)	1.03 (0.95–1.11)	1.01 (0.92–1.11)
M100	1.02 (1–1.04)	1.01 (0.99–1.03)	1.02 (1–1.04)	1.02 (1–1.05)	1.02 (0.99–1.04)	1.03 (0.99–1.06)
J-index	1.09 (1.01–1.18)[a]	1.05 (0.97–1.14)	1.1 (1.02–1.18)[a]	1.1 (1.004–1.2)[a]	1.09 (0.99–1.2)	1.13 (1.01–1.27)[a]
CONGA 1 h	1.09 (0.97–1.21)	1.07 (0.95–1.19)	1.15 (1.03–1.28)[a]	1.17 (1.03–1.33)[a]	1.13 (0.99–1.3)	1.04 (0.89–1.23)
CONGA 2 h	1.07 (0.98–1.16)	1.05 (0.97–1.14)	1.11 (1.02–1.21)[a]	1.13 (1.02–1.24)[a]	1.1 (0.99–1.22)	1.08 (0.96–1.23)
CONGA 3 h	1.06 (0.98–1.14)	1.05 (0.97–1.13)	1.08 (1.01–1.17)[a]	1.11 (1.02–1.22)[a]	1.09 (0.99–1.2)	1.1 (0.98–1.24)
CONGA 4 h	1.05 (0.98–1.13)	1.05 (0.97–1.12)	1.07 (1–1.14)	1.09 (1.01–1.19)[a]	1.08 (0.99–1.19)	1.11 (0.99–1.24)
CONGA 6 h	1.06 (0.99–1.14)	1.05 (0.98–1.13)	1.07 (1.003–1.15)[a]	1.08 (1.001–1.17)[a]	1.07 (0.98–1.17)	1.11 (1–1.23)

TABLE 4 Associations between continuous glucose monitoring parameters and adverse perinatal outcomes, univariable models (n = 102) (continued from the previous page)

Parameter	LGA	Hypoglycemia	Hyperbilirubinemia	Transient breathing disorders	Preterm birth	Pre-eclampsia
GRADE	1.35 (0.94–1.94)	1.17 (0.81–1.69)	1.37 (0.97–1.93)	1.5 (0.99–2.29)	1.36 (0.85–2.16)	1.51 (0.87–2.61)
GRADE eu	0.98 (0.92–1.03)	1 (0.94–1.05)	0.97 (0.92–1.02)	0.99 (0.93–1.05)	0.98 (0.92–1.05)	0.96 (0.88–1.05)
GRADE hypo	0.97 (0.94–0.99)[a]	0.99 (0.96–1.02)	0.98 (0.95–1.00)	0.98 (0.95–1.01)	0.97 (0.94–1.01)	0.95 (0.89–1.01)
GRADE hyper	1.04 (1.01–1.07)[a]	1.01 (0.99–1.04)	1.03 (1.01–1.06)[a]	1.02 (0.99–1.05)	1.03 (0.99–1.07)	1.05 (1.003–1.11)[a]
Third trimester						
Mean glucose	1.05 (1.02–1.09)[a]	1.02 (0.99–1.05)	1.04 (1.01–1.07)[a]	1.03 (1–1.06)	1.02 (0.99–1.06)	1.02 (0.98–1.06)
TAR	1.06 (1.02–1.1)[a]	1.01 (0.98–1.05)	1.04 (1.01–1.08)[a]	1.03 (0.99–1.07)	1.03 (0.99–1.07)	1.02 (0.97–1.06)
TIR	0.94 (0.91–0.98)[a]	0.99 (0.95–1.03)	0.96 (0.92–0.99)[a]	0.97 (0.93–1.01)	0.97 (0.93–1.02)	0.99 (0.94–1.04)
AUC	1.05 (1.02–1.09)[a]	1.02 (0.99–1.05)	1.04 (1.01–1.07)[a]	1.03 (1–1.06)	1.02 (0.99–1.06)	1.02 (0.98–1.06)
AUC over 140 mg/dl	1.13 (1.03–1.23)[a]	1.05 (0.98–1.12)	1.09 (1.01–1.18)[a]	1.06 (0.99–1.14)	1.03 (0.96–1.11)	1.01 (0.92–1.11)
HbA_{1c}	2.15 (1.06–4.39)[a]	1.24 (0.6–2.54)	1.94 (0.98–3.82)	1.63 (0.75–3.57)	1.75 (0.71–4.29)	3.27 (1.19–8.96)[a]
GMI	4.18 (1.57–11.12)[a]	1.66 (0.71–3.87)	3.04 (1.25–7.4)[a]	2.25 (0.9–5.65)	1.87 (0.69–5.11)	1.53 (0.5–4.73)
%CV	1.04 (0.94–1.16)	1.06 (0.94–1.18)	1.06 (0.96–1.18)	1 (0.88–1.13)	1.02 (0.88–1.17)	1.02 (0.87–1.19)
MAGE	1.03 (1.003–1.06)[a]	1.02 (0.99–1.04)	1.03 (1–1.05)	1.02 (0.99–1.05)	1.02 (0.99–1.05)	1.01 (0.97–1.04)
MODD	1.08 (1.015–1.14)[a]	1.03 (0.97–1.09)	1.06 (1.001–1.12)[a]	1.08 (1.01–1.15)[a]	1.05 (0.98–1.12)	0.99 (0.92–1.08)
LBGI	0.6 (0.36–0.99)[a]	0.87 (0.58–1.3)	0.69 (0.45–1.06)	0.77 (0.47–1.27)	0.76 (0.43–1.36)	0.6 (0.28–1.3)
HBGI	1.8 (1.18–2.76)[a]	1.27 (0.92–1.75)	1.54 (1.06–2.25)[a]	1.36 (0.97–1.91)	1.18 (0.83–1.69)	1.06 (0.69–1.64)
ADRR	1.02 (0.96–1.09)	1.03 (0.97–1.1)	1.04 (0.97–1.1)	1.04 (0.96–1.11)	1.03 (0.95–1.12)	0.94 (0.85–1.04)
M100	1.03 (1.006–1.05)[a]	1.01 (0.99–1.03)	1.02 (1.001–1.04)[a]	1.01 (1–1.03)	1.01 (0.99–1.03)	1 (0.97–1.02)
J-index	1.12 (1.04–1.22)[a]	1.05 (0.98–1.12)	1.1 (1.02–1.18)[a]	1.07 (0.99–1.15)	1.04 (0.97–1.12)	1.03 (0.94–1.12)
CONGA 1 h	1.08 (0.95–1.22)	1.07 (0.94–1.21)	1.14 (1.01–1.29)[a]	1.18 (1.02–1.36)[a]	1.11 (0.95–1.3)	0.89 (0.73–1.09)
CONGA 2 h	1.07 (0.98–1.17)	1.06 (0.96–1.16)	1.12 (1.02–1.22)[a]	1.1 (1–1.22)	1.08 (0.96–1.20)	0.98 (0.86–1.12)
CONGA 3 h	1.08 (1.00–1.17)	1.05 (0.97–1.14)	1.11 (1.02–1.2)[a]	1.08 (0.99–1.18)	1.05 (0.96–1.16)	1.02 (0.91–1.13)
CONGA 4 h	1.09 (1.01–1.17)[a]	1.05 (0.97–1.13)	1.1 (1.02–1.18)[a]	1.06 (0.98–1.15)	1.04 (0.95–1.14)	1.02 (0.92–1.13)
CONGA 6 h	1.08 (1.01–1.17)[a]	1.05 (0.98–1.13)	1.09 (1.01–1.17)[a]	1.05 (0.97–1.14)	1.04 (0.96–1.13)	1.04 (0.94–1.14)
GRADE	1.54 (1.1–2.15)[a]	1.18 (0.87–1.59)	1.41 (1.03–1.93)[a]	1.3 (0.95–1.8)	1.2 (0.84–1.71)	0.99 (0.64–1.55)
GRADE eu	0.96 (0.92–1.01)	1 (0.95–1.04)	0.97 (0.93–1.01)	0.99 (0.94–1.04)	0.99 (0.93–1.05)	1.01 (0.95–1.07)
GRADE hypo	0.96 (0.93–0.99)[a]	0.99 (0.97–1.02)	0.97 (0.94–1)	0.99 (0.96–1.02)	0.98 (0.94–1.02)	0.95 (0.89–1.01)
GRADE hyper	1.04 (1.01–1.07)[a]	1.01 (0.98–1.03)	1.03 (1.01–1.06)[a]	1.01 (0.99–1.04)	1.02 (0.99–1.05)	1.03 (0.99–1.07)

Data are presented as odds ratios (95% CIs).

a $P < 0.05$

Abbreviations: LGA, large-for-gestational-age; others, see **TABLE 2**

compared with the outcomes of the CONCEPTT randomized trial,[2] as we used the same methodology to calculate the birth weight percentiles. We believe that lower incidence of macrosomic (18%) and LGA (27%) births in our study cohort is directly associated with better glycemic control in comparison with other large studies.

We found significantly worse second- and third-trimester glycemic control defined by mean glucose levels, TIR, TAR, and HbA_{1c} values, and did not detect any differences in the CGM metrics in the first trimester between the mothers of LGA infants and non-LGA infants. Other studies reported significantly worse glycemic control (defined by mean glucose, TIR, and TAR values) in the mothers of LGA infants.[5,7,25] Moreover, the analyses of daily and weekly glycemic profiles indicated that the mothers of LGA infants had higher CGM mean glucose levels and spent markedly less time in target values from the 10th week of pregnancy.[25-27] It was proposed that the LGA risk is associated with other, less common CGM metrics, such as %CV, SD of mean sensor glucose values, MODD, and LBGI.[5-7,28] Finally, mean ponderal index values in the newborns of mothers with T1D correlated with the mean glycemia, SD of mean sensor glucose values, HBGI, and CONGA 1 h values.[29] We detected an association between the LGA risk and multiple parameters calculated using the data from late pregnancy. The observed relationships remained significant after adjustment for multiple confounders, which makes them promising tools for further clinical application.

We did not detect any significant differences in glycemic control and the relationship between

TABLE 5 Comparison of clinical parameters and continuous glucose monitoring indices between mothers of large-for-gestational-age and non-large-for-gestational-age newborns (n = 102)

Parameter		non-LGA (n = 74)	LGA (n = 28)	*P* value
Maternal age, y		30.7 (4.9)	30.6 (5.7)	0.88[a]
Duration of diabetes, y		14 (7.7)	15 (7.3)	0.57[a]
Gestational age at baseline, week		9 (7–11)	7 (6–9)	0.08[b]
Diabetes complications at baseline, n	Diabetic retinopathy	9	3	–
	Diabetic nephropathy	8	4	–
Prepregnancy BMI, kg/m^2		23.2 (21.3–26.9)	24.2 (21.4–27.3)	0.55[b]
Whole gestational weight gain, kg		12.3 (5.6)	14.5 (5.1)	0.07[a]
HbA_{1c}, %; mmol/mol	First trimester	6.19 (5.85–6.9); 44.2 (40.4–51.9)	6.48 (6.11–6.94); 47.3 (43.3–52.3)	0.14[b]
	Second trimester	5.39 (5.1–5.76); 35.4 (32.2–39.5)	5.77 (5.47–6.04); 39.6 (36.3–42.5)	0.01[b]
	Third trimester	5.69 (5.3–6.14); 38.7 (34.4–43.6)	6.04 (5.54–6.37); 42.5 (37.0–46.1)	0.03[b]
Triglycerides, mg/dl	First trimester	66.4 (49.5–85.2)	56.6 (46.4–75.2)	0.23[b]
	Second trimester	124.8 (102.6–168.3)	137.2 (94.6–151.7)	0.83[b]
	Third trimester	235.5 (185.9–288.5)	258.7 (208.7–331.1)	0.09[b]
Sensor mean glucose levels, mg/dl; mmol/l	First trimester	112.8 (102.6–120.5); 6.27 (5.7–6.69)	114.8 (107.5–124.3); 6.38 (5.97–6.91)	0.23[b]
	Second trimester	110.3 (103.1–120.1); 6.13 (5.73–6.67)	119.4 (112.5–131.2); 6.63 (6.25–7.29)	0.02[b]
	Third trimester	113.2 (104.4–123.1); 6.29 (5.8–6.84)	124 (113.3–131.9); 6.89 (6.29–7.33)	0.01[b]
TAR 140 mg/dl, %	First trimester	20.8 (11.5–26.9)	23.1 (16.2–32.5)	0.1[b]
	Second trimester	19.2 (11.4–29.2)	26.3 (19.3–36.2)	0.01[b]
	Third trimester	19.1 (11.8–28.6)	28.1 (17.6–36.1)	<0.01[b]
TIR 63–140 mg/dl, %	First trimester	72.9 (67.7–80.9)	71.8 (62.1–76.6)	0.17[b]
	Second trimester	74.6 (65–83)	69.6 (62.6–76.5)	0.04[b]
	Third trimester	77.1 (68.6–82.7)	69.9 (61.3–78.7)	0.01[b]
TBR 63 mg/dl, %	First trimester	4.4 (2.8–7.8)	5.0 (2.4–7.9)	0.68[b]
	Second trimester	4.6 (2.1–8)	3.8 (1.7–5.4)	0.18[b]
	Third trimester	2.7 (1.2–5.2)	2 (0.7–3.3)	0.13[b]
TBR 54 mg/dl, %	First trimester	1.4 (0.6–2.8)	1.7 (0.5–3)	0.98[b]
	Second trimester	1.6 (0.5–3.1)	1.2 (0.5–2.6)	0.34[b]
	Third trimester	0.6 (0.2–1.5)	0.5 (0.2–0.9)	0.15[b]

Data are presented as mean (SD) or median and interquartile range.

a *t* test **b** Mann–Whitney test

SI conversion factors: see **TABLE 2**

Abbreviations: see **TABLES 1**, **2**, and **4**

the CGM parameters and the risk of neonatal hypoglycemia in our study cohort. In contrast to those findings, other researchers detected significant associations between several CGM metrics, such as mean glucose, TIR, TAR, and SD of mean sensor glucose values, and the risk of neonatal hypoglycemia.[6,21] This may partially be explained by inconsistent definitions of neonatal hypoglycemia. While we defined neonatal hypoglycemia as blood glucose level below 40 mg/dl (2.2 mmol/l) in a single laboratory measurement performed at least 3 hours after birth, others used a 2.6 mmol/l cutoff value,[16] or included only the cases requiring intravenous glucose administration.[6,21] Nonetheless, the incidence of neonatal hypoglycemia in our cohort was similar to other studies.[2,16]

The incidence of preterm births in our study cohort (12.7%) was much lower than in the other large trials conducted in CGM users (26%–42%).[2,16] The most recent report suggests that the implementation of CGM systems significantly decreases the risk of preterm births in the population of patients with T1D.[20] We noted significantly decreased TIR and increased TAR values in the first trimester of pregnancy in the mothers of preterm infants. Moreover, regression outcomes suggest that a higher risk of preterm birth is linked to disturbances in the first-trimester glycemic parameters rather than insufficient glucose control in late pregnancy. Based on unadjusted regression models, Meek et al[6] reported that the risk of preterm birth was significantly associated with the first- and second-trimester mean glucose, TIR, and TAR levels. Only the relationship with TAR remained significant for the third-trimester data in that study.[6]

Our findings suggest that HbA_{1c} measurements are more reliable for the assessment of pre-eclampsia risk than CGM data. Interestingly,

TABLE 6 Comparison of clinical parameters and continuous glucose monitoring indices between mothers of neonates with hyperbilirubinemia treated with phototherapy and unaffected newborns (n = 102)

Parameter		Not affected (n = 68)	Hyperbilirubinemia (n = 34)	*P* value
Maternal age, y		31 (5.2)	30.2 (4.9)	0.47[a]
Duration of diabetes, y		14.7 (7.7)	13.6 (7.3)	0.54[a]
Gestational age at baseline, week		9 (6–11)	9 (7–11)	0.91[b]
Diabetes complications at baseline, n	Diabetic retinopathy	9	3	–
	Diabetic nephropathy	9	3	–
Prepregnancy BMI, kg/m^2		23.5 (21.2–26.7)	23.3 (21.6–26.9)	0.99[b]
Whole gestational weight gain, kg		12.5 (5.3)	13.8 (5.9)	0.27[a]
HbA_{1c}, %; mmol/mol	First trimester	6.28 (6.02–6.9); 45.1 (42.3–51.9)	6.12 (5.52–6.87); 43.4 (36.8–51.6)	0.18[b]
	Second trimester	5.46 (5.17–5.8); 36.2 (33–39.9)	5.71 (5.13–6.09); 38.9 (32.6–43.1)	0.39[b]
	Third trimester	5.72 (5.33–6.11); 39 (34.8–43.3)	5.95 (5.52–6.38); 41.5 (36.8–46.2)	0.08[b]
Triglycerides, mg/dl	First trimester	64.3 (47.5–83.3)	63.1 (52.2–83.7)	0.62[b]
	Second trimester	124 (98–157.9)	131.5 (106.6–175.2)	0.2[b]
	Third trimester	238.1 (193.4–315.2)	245.1 (203.6–282.4)	0.92[b]
Sensor mean glucose levels, mg/dl; mmol/l	First trimester	113 (104.8–121); 6.28 (5.82–6.72)	116.7 (107.5–120.6); 6.48 (5.97–6.7)	0.47[b]
	Second trimester	111.4 (104.9–119.5); 6.19 (5.83–6.64)	118.9 (106.2–127.9); 6.61 (5.9–7.11)	0.02[b]
	Third trimester	112.6 (104.4–123.4); 6.26 (5.8–6.86)	119.5 (113.2–129.5); 6.64 (6.29–7.19)	0.01[b]
TAR 140 mg/dl, %	First trimester	20.7 (12.4–27.4)	24.2 (15.3–26.9)	0.53[b]
	Second trimester	19.3 (12.2–26.6)	26.4 (16.3–34.5)	0.02[b]
	Third trimester	19.4 (11.8–29.4)	24.3 (17.6–36.4)	0.02[b]
TIR 63–140 mg/dl, %	First trimester	72.4 (12.4–27.4)	72.4 (62.6–26.9)	0.47[b]
	Second trimester	74.5 (67.1–79.2)	66.2 (62.2–80.2)	0.053[b]
	Third trimester	76.9 (68.6–83.8)	73.8 (61.2–79)	0.04[b]
TBR 63 mg/dl, %	First trimester	4.7 (2.8–8)	4.4 (2.7–6.9)	0.96[b]
	Second trimester	4.5 (2.1–7.7)	3.5 (2–6.2)	0.35[b]
	Third trimester	2.7 (1.1–5.1)	2.2 (0.7–3.5)	0.2[b]
TBR 54 mg/dl, %	First trimester	1.5 (0.5–2.9)	1.4 (0.7–2.6)	0.71[b]
	Second trimester	1.6 (0.5–2.9)	1.1 (0.4–2.6)	0.53[b]
	Third trimester	0.6 (0.2–1.5)	0.5 (0.1–1.3)	0.42[b]

Data are presented as mean (SD) or median and interquartile range.

a *t* test **b** Mann–Whitney test

SI conversion factors: see **TABLE 2**

Abbreviations: see **TABLES 1** and **2**

Meek et al[6] detected the association between the pre-eclampsia risk and the second-trimester mean glucose, TIR, TAR, and SD of mean sensor glucose values. They did not find those correlations using the first- and third-trimester data, which was consistent with our outcomes. Tiselko et al[30] discovered an association between the pre-eclampsia risk and MAGE, MODD, CV, and SD of mean sensor glucose values. They also reported that increased glycemic variability negatively correlated with the gestational age at the diagnosis of pre-eclampsia. Analyzing the influence of the CGM parameters on the pre-eclampsia risk, we need to be conscious of the elusive, multifactorial pathogenesis of pre-eclampsia. Despite the optimal glycemic control noted in our cohort, the incidence of pre-eclampsia was similar to the results of other trials.[2,16]

To our knowledge, we provided the first analysis of the potential determinants of neonatal hyperbilirubinemia and transient breathing disorders in the population of women with T1D using the CGM data. We noted a similar percentage of neonatal hyperbilirubinemia cases as in the CONCEPTT trial.[2] The authors of the CONCEPTT trial did not provide any definition of hyperbilirubinemia in their study group. We analyzed only the cases of clinically relevant neonatal jaundice requiring phototherapy. The previous studies analyzing CGM data in the pregnant patients with T1D did not assess the incidence of mild transient respiratory disorders in newborns. We demonstrated that the risk of neonatal hyperbilirubinemia is more strongly connected with the parameters of long-term glycemic control than with the risk of breathing disorders. In both situations, the disturbances observed in the second trimester of pregnancy had a more significant impact on the risk of adverse pregnancy outcomes than the data from early pregnancy.

TABLE 7 Comparison of clinical parameters and continuous glucose monitoring indices between mothers of term and preterm infants (n = 102)

Parameter		Term (n = 89)	Preterm (n = 13)	*P* value
Maternal age, y		30.7 (5)	30.9 (6)	0.87[a]
Duration of diabetes, y		14.1 (7.5)	15.4 (8.1)	0.62[a]
Gestational age at baseline, week		8 (6–11)	9 (7–11)	0.57[b]
Diabetes complications at baseline, n	Diabetic retinopathy	9	3	–
	Diabetic nephropathy	10	2	–
Prepregnancy BMI, kg/m^2		23 (21.3–26.9)	25.7 (23.8–27.7)	0.03[b]
Whole gestational weight gain, kg		13.1 (5.6)	11.3 (4.6)	0.26[a]
HbA_{1c}, %; mmol/mol	First trimester	6.26 (6–6.9); 44.9 (42.1–51.9)	6.02 (5.72–6.53); 42.3 (39–47.9)	0.33[b]
	Second trimester	5.46 (5.13–5.86); 36.2 (32.6–40.5)	5.71 (5.38–6.04); 38.9 (35.3–42.5)	0.17[b]
	Third trimester	5.73 (5.39–6.29); 39.1 (35.4–45.2)	5.9 (5.63–6.29); 41 (38–45.2)	0.33[b]
Triglycerides, mg/dl	First trimester	63.2 (48.4–84.5)	67 (54.7–76.3)	0.73[b]
	Second trimester	127.7 (100.7–161.7)	126.4 (104–137.3)	0.86[b]
	Third trimester	247.9 (197.8–312.7)	218.9 (181–282)	0.36[b]
Sensor mean glucose levels, mg/dl; mmol/l	First trimester	113 (103–120.6); 6.28 (5.72–6.7)	119.2 (111.6–132.6); 6.62 (6.20–7.37)	0.06[b]
	Second trimester	114.2 (104.9–123.5); 6.34 (5.83–6.86)	117 (115.4–132.1); 6.5 (6.41–7.34)	0.09[b]
	Third trimester	114.1 (106.1–124.9); 6.34 (5.89–6.94)	118 (112.6–125.4); 6.56 (6.26–6.97)	0.29[b]
TAR 140 mg/dl, %	First trimester	20.1 (12.2–27)	26.7 (24.2–39.8)	0.01[b]
	Second trimester	20.1 (12.4–30.5)	25 (21.9–36.2)	0.16[b]
	Third trimester	20.3 (12.9–30.7)	25.1 (17.5–30.1)	0.30[b]
TIR 63–140 mg/dl, %	First trimester	75.1 (67.6–81)	67.6 (57.5–71.5)	<0.01[b]
	Second trimester	73.3 (64.8–80.4)	71.3 (62.6–74.6)	0.19[b]
	Third trimester	76 (67.4–81.9)	69.9 (62.5–80.6)	0.38[b]
TBR 63 mg/dl, %	First trimester	4.4 (2.8–7.7)	5.2 (1.8–12.3)	0.74[b]
	Second trimester	4.2 (2–7.5)	4.6 (2.3–5.5)	0.8[b]
	Third trimester	2.6 (1–4.4)	2.1 (0.7–4.9)	0.79[b]
TBR 54 mg/dl, %	First trimester	1.5 (0.7–2.7)	2.2 (0.4–5.6)	0.64[b]
	Second trimester	1.5 (0.5–2.8)	1.7 (0.7–2.6)	0.99[b]
	Third trimester	0.6 (0.2–1.4)	0.5 (0.2–1.3)	0.6[b]

Data are presented as mean (SD) or median and interquartile range.

a *t* test **b** Mann–Whitney test

SI conversion factors: see **TABLE 2**

Abbreviations: see **TABLES 1** and **2**

Study strengths and limitations The study's greatest strength is the fact that we were able to recruit the largest number of pregnant women on sensor-augmented insulin pump treatment of all other large studies.[2,3,5] This may be explained by our intensive management protocol, including 3 hospitalizations, routine follow-up visits to the diabetes and gynecology clinic, and donation of the devices by the charity foundation. Thanks to this protocol, such good results could be obtained. The retrospective recruitment of the study participants and data collection from electronic medical records could be considered the first weak point of the study. The number of recruited study participants was sufficient to conduct a relatively well-powered analysis in the subgroups with LGA, hyperbilirubinemia, and hypoglycemia. However, in the subgroups we observed a relatively small number of patients with neonatal transient breathing disorders, preterm births, and pre-eclampsia. The limited statistical power of those between-group comparisons and all of the multivariable analyses should be interpreted as an important study limitation. The weakness of the study was the time of using the sensor by some study participants. In general, they used the sensors irregularly without any specific reason, or decided to change the mode of therapy to multiple daily injections for several days, or experienced some other temporary technical issues with their sensor-augmented pumps. Our study group was ethnically homogenous and derived from a single tertiary referral university clinic, which may raise concerns about the generalizability of the data to other regions, ethnic groups, and health care systems. Exclusion of the patients with multiple pregnancies could have influenced the explanatory values of the investigated parameters in the general population. Moreover, the study outcomes cannot be directly compared with those in the patients who are

TABLE 8 Comparison of clinical parameters and continuous glucose monitoring indices in women with and without pre-eclampsia (n = 102)

Parameter		Healthy (n = 92)	Pre-eclampsia (n = 10)	*P* value
Maternal age, y		30.8 (5.1)	30 (5.8)	0.65[a]
Duration of diabetes, y		15 (8–20)	19 (9–22)	0.41[b]
Gestational age at baseline, week		9 (6–11)	8 (7–10)	0.9[b]
Diabetes complications at baseline, n	Diabetic retinopathy	9	3	–
	Diabetic nephropathy	9	3	–
Prepregnancy BMI, kg/m^2		23.2 (21.3–27)	24.8 (21.6–26.8)	0.67[b]
Whole gestational weight gain, kg		12.8 (5.5)	13.5 (5.7)	0.72[a]
HbA_{1c}, %; mmol/mol	First trimester	6.19 (5.87–6.74); 44.2 (40.7–50.2)	6.91 (6.69–7.11); 52 (49.6–54.2)	0.01[b]
	Second trimester	5.46 (5.14–5.8); 36.2 (32.7–39.9)	6.23 (5.64–6.44); 44.6 (38.1–46.9)	0.01[b]
	Third trimester	5.72 (5.34–6.18); 39 (34.9–44)	6.4 (5.74–6.79); 46.4 (39.2–50.7)	0.02[b]
Triglycerides, mg/dl	First trimester	63.3 (48.4–84.5)	65.7 (59.3–73)	0.69[b]
	Second trimester	126.4 (99.1–160.3)	132 (104–174)	0.51[b]
	Third trimester	240.7 (195.4–292.9)	247.5 (206.6–313.8)	0.67[b]
Sensor mean glucose levels, mg/dl; mmol/l	First trimester	112.8 (103.5–120.5); 6.27 (5.75–6.69)	120.8 (113–127.1); 6.71 (6.28–7.06)	0.15[b]
	Second trimester	114.2 (104.9–122.7); 6.34 (5.83–6.82)	120.5 (116.2–132.7); 6.69 (6.46–7.37)	0.03[b]
	Third trimester	114.1 (105.6–125.7); 6.34 (5.87–6.98)	117.4 (113.5–125.4); 6.52 (6.31–6.97)	0.26[b]
TAR 140 mg/dl, %	First trimester	20.7 (13.4–26.9)	29 (21–31.9)	0.11[b]
	Second trimester	20.1 (12.8–29.7)	26.3 (23.1–36.2)	0.06[b]
	Third trimester	19.7 (12.7–31.5)	22.9 (20.7–30)	0.23[b]
TIR 63–140 mg/dl, %	First trimester	73.9 (67.9–80.4)	67.4 (64.7–71.7)	0.1[b]
	Second trimester	74.4 (65–80.3)	70.7 (58.4–72)	0.1[b]
	Third trimester	76.7 (66.8–82.1)	74.8 (68–76.2)	0.41[b]
TBR 63 mg/dl, %	First trimester	4.3 (2.7–7.9)	5.4 (3.5–7.3)	0.69[b]
	Second trimester	4.2 (1.9–7.6)	4.6 (2.4–4.9)	0.47[b]
	Third trimester	2.6 (1–4.9)	2.3 (1–2.9)	0.38[b]
TBR 54 mg/dl, %	First trimester	1.5 (0.5–2.9)	1.8 (1–2.6)	0.8[b]
	Second trimester	1.5 (0.5–3)	1.6 (0.6–1.7)	0.35[b]
	Third trimester	0.6 (0.2–1.5)	0.4 (0.2–0.7)	0.2[b]

Data are presented as mean (SD) or median and interquartile range.

a *t* test **b** Mann–Whitney test

SI conversion factors: see **TABLE 2**

Abbreviations: see **TABLES 1** and **2**

not admitted for regular hospital control visits throughout gestation. While our patients used the pumps with predictive low-glucose management, the first positive reports from trials on the pumps with automated insulin delivery (AID) in the pregnant population have been published.[31,32] The use of pumps with AID could restrict the overcorrection of the currently used systems and open new perspectives for better glycemic control in the patients with T1D. Our study cohort included only patients with T1D. Due to increasing prevalence of T2D in the Polish citizens, it would be interesting to investigate the clinical aspects of CGM use in that population.[33,34]

Conclusions Several less commonly used CGM parameters, such as MODD, HBGI, GRADE, or CONGA could be useful as additional tools in the prediction of pregnancy-related adverse outcomes in the patients with T1D treated with insulin pumps and CGM devices. However, we did not find any evidence that a range of novel CGM indices would be more effective than the commonly used CGM parameters, such as TIR, TAR, TBR, or mean glucose values or HbA_{1c} measurements. The effect sizes were small, as also observed by other investigators.[35] Based on that, their independent clinical relevance in the pregnant population is currently insufficient. The use of composite maternal and neonatal complication scores,[35] and/or combined CGM indices may also increase their predictive value, especially in the context of more advanced AID systems. Worse glycemic control in the second and third trimester, rather than early pregnancy results, was mainly associated with the increased risk of analyzed adverse perinatal outcomes. Our findings suggest that maternal CGM metrics reflecting glucose fluctuations attributed to hyperglycemic spikes

were more strongly associated with an increased risk of LGA at birth, neonatal transient breathing disorders, hyperbilirubinemia, and preterm births than with neonatal hypoglycemia, or pre-eclampsia. We believe that a reasonable clinical decision-making process regarding the pregnant patients with T1D should be based on the analysis of both CGM data and HbA_{1c} values.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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