DIABETES TECHNOLOGY & THERAPEUTICS
Volume 24, Number 8, 2022

DOI: 10.1089/dia.2021.0479

ORIGINAL ARTICLE

Hypoglycemia in Prospective Multicenter Study of Pregnancies with Pre-Existing Type 1 Diabetes on Sensor-Augmented Pump Therapy: The LOIS-P Study

Ravinder Jeet Kaur, MBBS,[1] Byron H. Smith, PhD,[2] Basak Ozaslan, PhD,[3] Jordan E. Pinsker, MD,[4] Mari Charisse Trinidad, MD,[1] Grenye O'Malley, MD,[5] Donna Desjardins, APRN, CNP, MS,[1] Kristin N. Castorino, DO,[4] Camilla Levister, NP,[5] Corey Reid, BS,[1] Shelly McCrady-Spitzer, MS,[1] Selassie J. Ogyaadu, MD, MPH,[5] Mei Mei Church, NP,[4] Molly Piper, BS,[4] Walter K. Kremers, PhD,[2] Barak Rosenn, MD,[5] Francis J. Doyle III, PhD,[3] Eyal Dassau, PhD,[3] Carol J. Levy, MD,[5] and Yogish C. Kudva, MD[1]

Abstract

Background: Pregnancies in type 1 diabetes are high risk, and data in the United States are limited regarding continuous glucose monitoring (CGM)-based hypoglycemia throughout pregnancy while on sensor-augmented insulin pump therapy.

Materials and Methods: Pregnant women with type 1 diabetes in the LOIS-P Study (Longitudinal Observation of Insulin use and glucose Sensor metrics in Pregnant women with type 1 diabetes using continuous glucose monitors and insulin pumps) were enrolled before 17 weeks gestation at three U.S. centers and we used their personal insulin pump and a study Dexcom G6 CGM. We analyzed data of 25 pregnant women for CGM hypoglycemia based on international consensus guidelines for percentage time <63 and 54 mg/dL, hypoglycemic events and prolonged hypoglycemia events for 24-h, daytime, and overnight periods, and severe hypoglycemia (SH) episodes.

Results: For a 24-h period, biweekly median percentage of time <63 mg/dL ranged from 0.8% at biweek 4–5 to 3.7% at biweek 14–15 with high variability throughout pregnancy. Median percentage of time <63 and 54 mg/dL was higher overnight than daytime ($P < 0.01$). Hypoglycemic events occurred throughout the pregnancy, ranged 1–4 events per 2 weeks, significantly decreased after the 20th week, and occurred predominantly during daytime ($P < 0.01$). For overnight period, hypoglycemia and events were more concentrated from 12 to 3 am. Seven prolonged hypoglycemia events without any associated SH occurred in four participants (16%), primarily overnight. Three participants experienced a single episode of SH.

[1]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota, USA.
[2]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA.
[3]Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Minnesota, USA.
[4]Sansum Diabetes Research Institute, Santa Barbara, California, USA.
[5]Division of Endocrinology, Diabetes and Metabolism and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, New York, USA.

Preliminary data were previously presented at American Diabetes Association 80th Scientific Sessions. June 2020. Poster 17-LB.

Conclusions: Our results suggest a higher overall risk of hypoglycemia throughout pregnancy during the overnight period with continued daytime risk of hypoglycemic events in pregnancies complicated by type 1 diabetes.

Keywords: Pregnancy, Type 1 diabetes, Hypoglycemia, Prolonged hypoglycemia, Continuous glucose monitoring.

Introduction

Pregnancy in women with pre-existing type 1 diabetes is associated with increased risk of maternal and fetal complications.[1–5] Stringent control of blood glucose levels has been demonstrated to reduce the risk of adverse maternal and fetal events,[6–8] and various stakeholder subspecialty organizations have proposed tight glycemic control targets to improve maternal and fetal outcomes.[9–12] With current technology, achieving strict glycemic control increases the risk of hypoglycemia as a result of decreasing hyperglycemia.

Glucose targets were initially recommended based on fingerstick testing without significant experience with and analysis of continuous glucose monitoring (CGM) data.[9–12] A recent international consensus CGM target statement proposes >70% time in range (TIR) of 63–140 mg/dL during pregnancy in women with type 1 diabetes.[13] Before the recommendations of these CGM targets, the multicenter CONCEPTT study, which evaluated glucose variability in patients randomized to capillary glucose monitoring with or without CGM (Guardian Real time or MiniMed Minilink system) use, demonstrated clinical benefits and safety of CGM use.[6] Pregnant CGM users spent more time in pregnancy-specific target range (68% vs. 61%) and less time in hyperglycemic range (27% vs. 32%) and hypoglycemic range (<70 mg/dL, 3% vs. 4%) than pregnant control type 1 diabetes participants, with comparable severe hypoglycemia (SH) episodes (18 in CGM and 21 in control cohorts respectively). CGM use in CONCEPTT also improved neonatal outcomes along with lowering glycated hemoglobin (HbA1c) at 34 weeks gestation.

In a longitudinal study utilizing intermittent continuous glucose monitoring (iCGM; Freestyle Libre) and real-time continuous glucose monitoring (rtCGM; with Dexcom G4) in pregnant women with type 1 diabetes, Kristensen et al. reported that elevated mean glucose levels, less time in target range, and increased glucose variability were associated with large for gestational age babies and adverse neonatal outcomes.[14] Participants using rtCGM throughout pregnancy spent less time below target range: particularly in the second and third trimester compared with iCGM users. rtCGM technology provides real-time glucose readings, alerts, and insight into current glucose control, permitting users to respond to unacceptable glycemic changes or trends in real time.

With further maturation of diabetes technology and the continued need to lessen the burden for pregnant women with type 1 diabetes, we used the most advanced rtCGM (Dexcom G6) prospectively at three clinical centers in the United States from enrollment at <17 weeks gestation through the end of pregnancy as part of a longitudinal observation of insulin use and CGM metrics in pregnant women with type 1 diabetes (LOIS-P study).[15] The Dexcom G6 CGM provides high accuracy with a mean absolute relative difference <10%, factory calibration, 10-day wear, and no acetaminophen interference. Thus, it has several advantages over the CGM used in CONCEPTT and Kristensen et al. studies.[14] A recent study done by Castorino et al. established accuracy and safety of Dexcom G6 CGM system use in pregnant women with diabetes.[16] In this article, we report our findings for hypoglycemia based on several current definitions for CGM data during pregnancy to comprehensively assess the burden of hypoglycemia in pregnancies with type 1 diabetes.

Materials and Methods

The study was conducted at Mayo Clinic, Rochester, MN, Sansum Diabetes Research Institute, Santa Barbara, CA, and the Icahn School of Medicine at Mount Sinai, NY, after central institutional review board (Mayo Foundation) approval. Written informed consent was obtained from all participants before enrollment.

Study population

At three U.S. centers, we prospectively evaluated and report on 25 completed pregnancies utilizing study Dexcom G6 continuous glucose monitor (Dexcom, Inc., San Diego, CA) and their personal insulin pump with enrollment in the LOIS-P study.[15] This is a secondary analysis with detailed inclusion and exclusion criteria of this study mentioned under the LOIS-P study.[15]

Pregnant women with a history of type 1 diabetes for at least a year were enrolled before 17 weeks gestational age. Participants were contacted regularly through scheduled follow-up visits either in person or on the telephone until the last postpartum visit. CGM and blood glucose meter data were downloaded regularly along with personal insulin pump data for analysis.[15]

Statistical analyses

This is a secondary analysis of LOIS-P article that has provided analyses of CGM metrics, insulin use, and carbohydrate intake data across the same participants. The result of the LOIS-P article demonstrated changing patterns of CGM, TIR, time above range, and time below range during pregnancy. The time below range (<63 mg/dL) was 3% ± 3% in the LOIS-P study. There are limited studies available in the field that describe the risk of hypoglycemia throughout pregnancy.

Hence, this article focuses on CGM-based hypoglycemia, hypoglycemic events, and prolonged hypoglycemic events to assess the burden of hypoglycemia in pregnancies with

type 1 diabetes in this closely followed sensor-augmented insulin pump (SAP) cohort.[15] To quantify hypoglycemia, we evaluated CGM data biweekly (per group per 2 weeks) throughout pregnancy using the following metrics as recommended by International Consensus on CGM reporting for three time blocks: 24 h, daytime, and nighttime.[13,17]

- Percentage time CGM glucose <63and <54 mg/dL.
- Number of hypoglycemic events defined as CGM glucose of <54 mg/dL for at least three consecutive measurements (≥15 min) followed by three consecutive readings ≥70 mg/dL.
- Number of prolonged hypoglycemic events defined by CGM glucose of <54 mg/dL for at least 24 consecutive measurements (≥120 min) followed by at least three consecutive readings (≥15 min) ≥70 mg/dL.
- SH episodes were also reported and defined as cognitive impairment requiring active assistance from a third party for recovery.

Consecutive events were defined by taking runs of CGM data that were separated by no more than 10 min. For example, measurements recorded at 5:00 and 5:05 pm would be considered consecutive while measurements at 5:00 and 5:11 pm with a glucose value missing in between would not be considered consecutive. Within each run of consecutive CGM measurements, hypoglycemic events (15 consecutive minutes) and prolonged events (120 consecutive minutes) could be defined only after that respective amount of time had lapsed.

After defining consecutive runs of measurements for each patient, the measures above were summarized by predefined daily time periods: (1) 24 h, (2) daytime (6 to 12 am), or (3) overnight (12 to 6 am) using median and interquartile range (IQR) for event counts or percentages every 2 gestational weeks (14 days), starting at 4 to 5 weeks along with describing distribution of hypoglycemia hour by hour over the 24 h. For the hour-by-hour description, we did not conduct statistical significance testing. A biweekly data set is counted as days 0 to 13, then days 14 to 27, and so on for every 2 weeks.

Values are presented as median (IQR) for quantitative data. Linear mixed-effects model was used for percentage under 63 and 54 mg/dL and generalized linear mixed effects model with a Poisson regression for counts of events to evaluate statistical significance of the change between gestational age in biweek based on the reference gestational biweek that was selected as 12 weeks 0 days to 13 weeks 6 days.[15] Reference biweek 12–13 was chosen based on being the earliest available time with >75% of the cohort represented to reduce the risk of higher bias due to the small sample size and the potential in early pregnancy of rapid dosing adjustments after the confirmation of pregnancy to improve glycemic control.

In addition, the end of the first trimester has been described as a relatively stable interval in previous literature.[18–20] This method accounts for multiple measurements per person by using a random effect for patient and accurately model the zero-heavy nature of data.[21–23] Locally weighted scatterplot smoothing (LOESS) was used to visually demonstrate temporal hypoglycemic trends. A P value of <0.05 was considered statistically significant. Comparisons between biweeks are summarized for each measure of hypoglycemia and come from a single mixed effects model without P value adjustment. The reference level biweek (weeks 12 and 13) was chosen before analysis (justified above). All analyses were performed in R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We report data from 25 pregnant women with type 1 diabetes with mean age of 30.2 ± 4.8 years and enrollment HbA1c of 6.6% ± 0.9% (for further demographics see Supplementary Table S1). Gestational weeks at enrollment and delivery were 11.2 ± 3.9 and 37.7 ± 1.6, respectively. As participants were enrolled at variable gestational ages, the valid data set (CGM data for >20 h within each 24-h period) available after 14–15 weeks was greater than that for earlier weeks.

CGM glycemic metrics: percentage time below targets

Biweekly: percentage time <63 and <54 mg/dL (Fig. 1)

Twenty-four-hour period: The median percentage of time CGM glucose <63 and 54 mg/dL is presented in Table 1. A significant decrease in median percentage of time <63 mg/dL was seen during gestational biweek 26–27 (1.5%, $P = 0.01$), 28–29 (1.3%, $P = 0.04$), and 32–33 (1.3%, $P = 0.03$) compared with the reference biweek 12–13 (2.3%). A significant decrease in median percentage time <54 mg/dL was seen during gestational biweek 26–27 (0.12%, $P = 0.01$) and 32–33 (0.2%, $P = 0.04$) compared with reference biweek (0.9%) (Fig. 1).

Overnight (12–6 am) versus daytime (6–12 am) (Fig. 1): Throughout the study, participants spent an average of 1.36% more time <63 mg/dL ($P < 0.01$) and 0.78% more time <54 mg/dL ($P < 0.01$) overnight compared with daytime (Supplementary Table S2).

For the overnight period, there was no significant change in median percentage time <63 or 54 mg/dL across the pregnancy compared with the reference biweek (Table 1). Daytime biweekly median percentage time <63 mg/dL was significantly decreased during biweeks 22–23 and 26 weeks onward with exceptions of biweeks 34–35 and 38–39 compared with the reference biweek. Biweekly median percentage time <54 mg/dL was significantly decreased for 22–23, 26–27, 30–31, and 32–33 gestational biweeks compared with the reference biweek (Table 1).

Percentage of time CGM glucose <63 and 54 mg/dL by time of day: For percentage of time <63 mg/dL, more time was spent <63 mg/dL during early overnight period (12–3 am), and during daytime, it was more prominent between 4 and 7 pm than the rest of the day. For percentage time <54 mg/dL, more time was spent <54 mg/dL during early hour of the overnight period too and was similar during the daytime (Fig. 2).

CGM glycemic metrics: biweekly hypoglycemic events

Hypoglycemic event: <54 mg/dL with three consecutive readings (≥15 min) followed by three consecutive readings ≥70 mg/dL (Fig. 3)

Twenty-four-hour period (Fig. 3): The median events per 24-h period per biweek ranged from one to four events (Table 2). Hypoglycemic events significantly decreased for

Table 1. Biweekly: Percentage Time <63 and 54 mg/dL During Pregnancy

		24 h				*Overnight (12–6 am)*				*Daytime (6–12 am)*			
Gestational week	N	*% <63 mg/dL*	P	*% <54 mg/dL*	P	*% <63 mg/dL*	P	*% <54 mg/dL*	P	*% <63 mg/dL*	P	*% <54 mg/dL*	P
4–5	3	0.8 (0.7, 0.9)	0.49	0.1 (0.1, 0.2)	0.51	0 (0, 0.2)	0.70	0 (0, 0.1)	0.67	1 (0.8, 1.1)	0.44	0.1 (0.1, 0.3)	0.48
6–7	7	1.3 (1.1, 2.8)	0.70	0.2 (0, 0.9)	0.39	2.1 (0, 3.3)	0.62	0 (0, 1.5)	0.50	1.6 (1.1, 2.7)	0.86	0.2 (0.1, 0.7)	0.45
8–9	8	2.3 (1.9, 4.4)	0.59	0.5 (0.4, 1.9)	0.73	2.7 (1.2, 4.3)	0.65	0.5 (0, 1.1)	0.99	2.8 (1.1, 5)	0.65	0.7 (0.3, 2.3)	0.61
10–11	11	2.9 (2.7, 3.6)	0.42	0.7 (0.4, 1)	0.76	3.3 (0.9, 5.7)	0.20	1 (0, 1.4)	0.92	2.8 (2, 4.5)	0.81	0.6 (0.5, 1.1)	0.58
12–13§	19	2.3 (1.7, 4.8)	—	0.9 (0.4, 2)	—	2.7 (0.9, 5.1)	—	0.7 (0.2, 1.9)	—	2.4 (2.1, 4.7)	—	1 (0.4, 1.9)	—
14–15	24	3.7 (1.3, 7.6)	0.10	0.7 (0.2, 2.6)	0.20	2.7 (0.7, 8.9)	0.40	0.6 (0, 2.6)	0.94	2.7 (1.7, 7.1)	0.14	0.7 (0.2, 2.5)	0.14
16–17	25	2.8 (1.1, 4.7)	0.97	0.9 (0.2, 1.6)	0.93	2.5 (0.7, 5.6)	0.95	0.5 (0.1, 2.4)	0.96	2.2 (1.4, 5)	0.95	0.5 (0.1, 1.9)	0.87
18–19	25	2.1 (0.9, 3.3)	0.52	0.6 (0.2, 1.2)	0.82	1.3 (0, 3.1)	0.80	0.5 (0, 1.2)	0.98	2.1 (0.9, 3.6)	0.46	0.7 (0.1, 1.2)	0.79
20–21	25	2.2 (1, 3.7)	0.35	0.5 (0.2, 1.1)	0.26	1.8 (0.8, 5.8)	0.90	0.5 (0, 2.1)	0.90	1.8 (0.8, 4.1)	0.16	0.4 (0.1, 0.8)	0.12
22–23	25	1.8 (0.8, 3.1)	0.08	0.5 (0.1, 1)	0.09	2.4 (1.1, 4.6)	0.64	0.9 (0.1, 1.6)	0.53	1.1 (0.5, 3.1)	**0.03**‡	0.2 (0.1, 1)	**0.04**‡
24–25	25	1.9 (0.9, 4)	0.13	0.4 (0.2, 1.3)	0.26	2.2 (0.1, 4.2)	0.35	0.6 (0, 1.3)	0.26	1.5 (0.7, 4.2)	0.12	0.4 (0.1, 1.2)	0.40
26–27	25	1.5 (0.8, 2.5)	**0.01**‡	0.4 (0.1, 0.6)	**0.01**‡	1.7 (0.5, 2.3)	0.11	0.3 (0, 0.7)	0.08	1.2 (0.6, 3.2)	**0.01**‡	0.2 (0, 0.6)	**0.02**‡
28–29	25	1.3 (0.7, 2.9)	**0.04**‡	0.3 (0, 0.9)	0.09	1.5 (0.4, 3.2)	0.32	0.2 (0, 0.8)	0.33	1.4 (0.6, 2.6)	**0.02**‡	0.3 (0, 1)	0.08
30–31	25	2.2 (0.9, 4.6)	0.14	0.5 (0.1, 1.4)	0.16	2.5 (1.2, 6.1)	0.96	0.9 (0.2, 2.6)	0.91	1.4 (0.5, 3.7)	**0.03**‡	0.3 (0.1, 0.9)	**0.03**‡
32–33	24	1.3 (0.6, 2.5)	**0.03**‡	0.2 (0, 0.8)	**0.04**‡	1.8 (0.5, 4.9)	0.69	0.4 (0, 1)	0.39	1.2 (0.5, 1.7)	**0.00**‡	0.1 (0, 0.4)	**0.02**‡
34–35	24	2.1 (0.6, 5.2)	0.41	0.8 (0.2, 1.3)	0.26	4.1 (0.1, 7.9)	0.64	1.3 (0, 2.7)	0.95	1 (0.5, 4)	0.13	0.2 (0, 1)	0.11
36–37	20	1.6 (0.6, 3.9)	0.13	0.3 (0, 1.3)	0.10	2.4 (0.3, 7.3)	0.93	0.6 (0, 2.7)	0.54	1.4 (0.5, 3.2)	**0.03**‡	0.2 (0, 0.6)	0.05
38–39	12	2.9 (1.2, 9.4)	0.25	0.6 (0.3, 3.7)	0.42	2.8 (1.5, 10)	0.15	0.4 (0.2, 5.6)	0.15	2.8 (1, 9.1)	0.47	0.7 (0.4, 3.1)	0.80

Results are given as median (IQR) for quantitative data.

N = number of participants biweekly.

Linear mixed-effects model was used to evaluate the statistical significance changes over gestation biweeks in comparison with the reference gestational biweek (12 weeks 0 days to 13 weeks 6 days, indicated by symbol §). Statistical significance threshold of <0.05 is indicated by symbol ‡.

IQR, interquartile range.

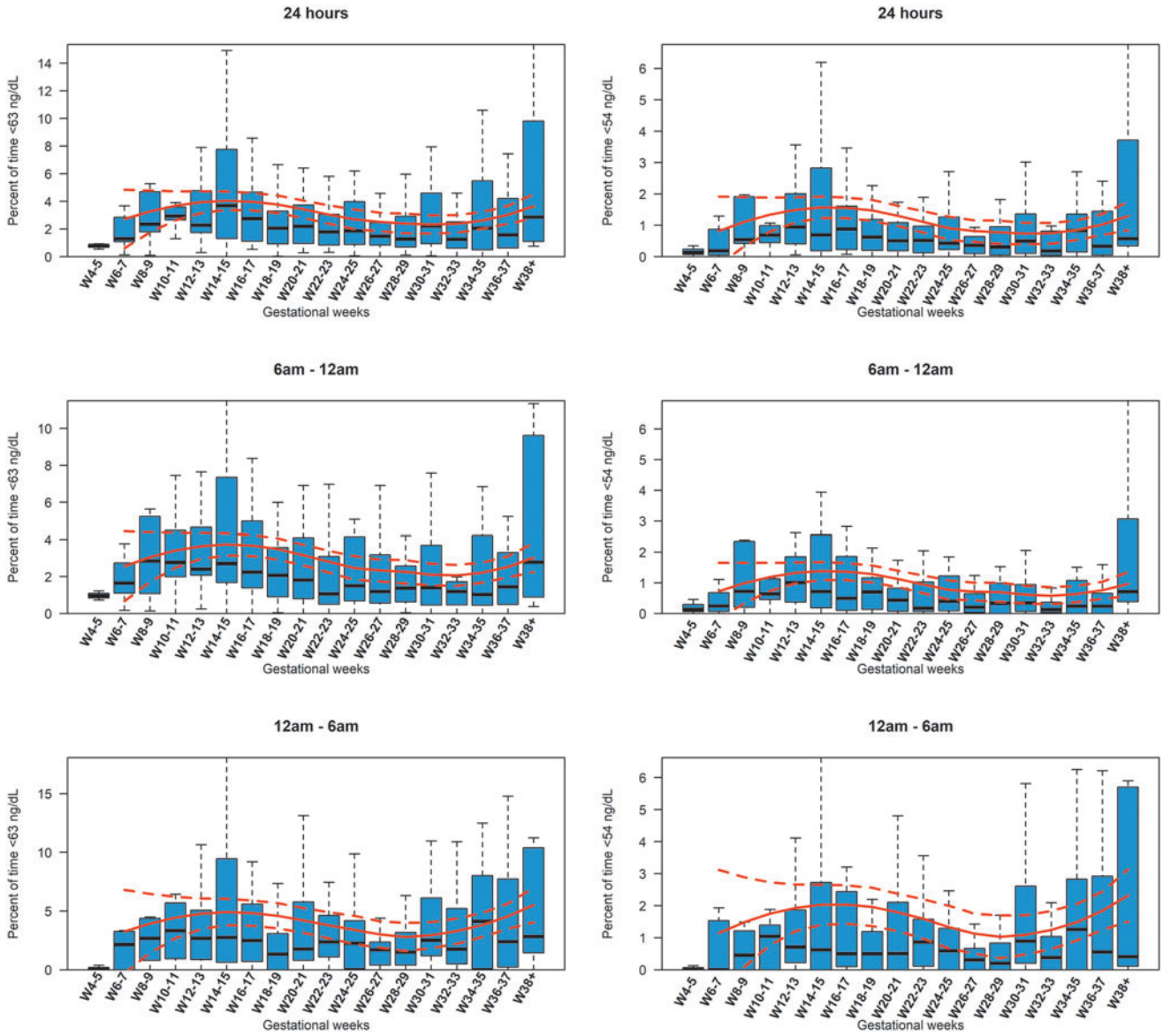

FIG. 1. Median percentage of time (IQR) <63 and 54 mg/dL biweekly (24 h, 18 h [6–12 am], and 6 h [12–6 am] time blocks). Participants spent more percentage time <63 and 54 mg/dL overnight (12–6 am) compared with daytime (6–12 am). LOESS spline (red color) curve goes through the mean. Kindly note the LOESS spline line does not extend all the way left to some of the biweeks. This is because the spline cannot estimate the actual curve with so few patients. IQR, interquartile range; LOESS, (Locally weighted scatterplot smoothing) is a nonparametric technique that uses local weighted regression to fit a smooth curve through points in a scatter plot, that help to see relationship between variables and foresee trends.

biweek 6–7 and for all weeks after 20–21 weeks (Table 2). Mean duration of hypoglycemic events is shown in Supplementary Table S3.

Overnight (12–6 am) and daytime (6–12 am) (Fig. 3): Throughout the study period, participants experienced an average of 0.13 more hypoglycemic events during daytime ($P < 0.01$) compared with overnight (Supplementary Table S2).

Daytime hypoglycemic events decreased significantly for biweek 6–7 and after biweek 18–19 through the end of the pregnancy. There was no significant change in overnight events except for biweek 26–27 that had a lower number of events compared with the reference biweek (Table 2). Mean duration of hypoglycemic events during daytime and overnight is shown in Supplementary Table S3.

Every participant in the study had hypoglycemic events (Supplementary Table S4). Four participants were enrolled at the beginning of the second trimester; hence there are no data for four enrollees during the first trimester. All the participants experienced hypoglycemic events in the second trimester, whereas 95% of participants had these events in the first and third trimesters. Median number of hypoglycemic events per patient per biweek in each trimester is given in Supplementary Table S5 and decreased significantly by the third trimester.

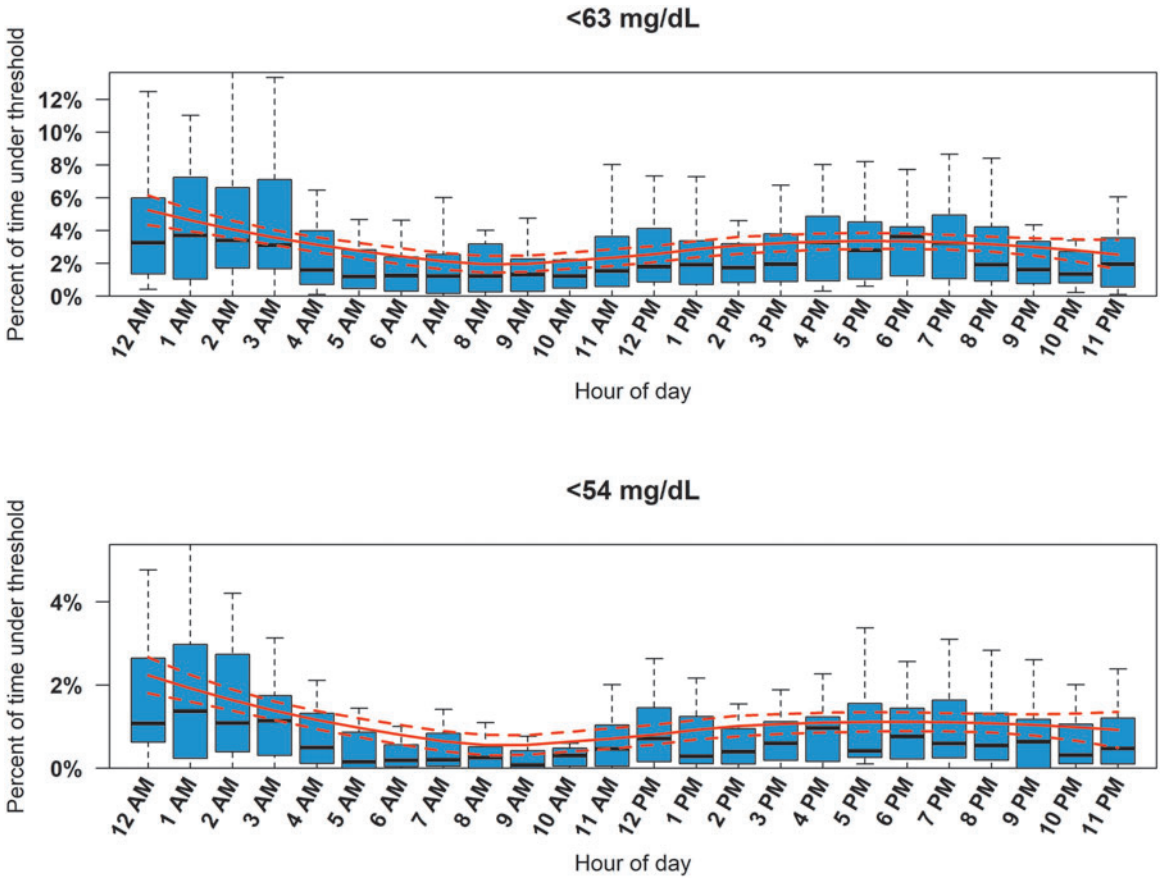

FIG. 2. Median percentage of time (IQR) CGM glucose <63 and 54 mg/dL by time of day. LOESS spline (red color) curve goes through the mean. CGM, continuous glucose monitoring.

Hypoglycemic events by time of day: During the overnight period, more hypoglycemic events were seen during the early hours between 12 and 3 am than between 3 and 6 am. During the daytime, more events were seen around 11–12 pm, 3 to 8 pm, and at 11 pm (Fig. 4).

Prolonged hypoglycemic event: <54 mg/dL for ≥120 consecutive minutes followed by three consecutive readings ≥70 mg/dL (Table 3)

A total of 18 prolonged hypoglycemia events were observed throughout pregnancy in four participants. Of those, 11 events were artifactual due to positional effect as there was no clinical hypoglycemia experienced by the participant, and there was an increase in glucose on CGM without any carbohydrate intake (patient self-report during clinical encounter) or decrease in insulin delivery, whereas 7 were confirmed hypoglycemic events. For analysis, we have removed the 11 artifactual events and analyzed the 7 confirmed prolonged hypoglycemic events (Table 3). Maximum prolonged hypoglycemic events occurred during biweeks 18–19 (two events). Most prolonged hypoglycemic events were observed overnight (a total of six events from three participants) compared with daytime (one event from one participant). Mean duration of prolonged hypoglycemic events during daytime and overnight is shown in Supplementary Table S6. These values are the average per biweekly per patient.

Severe hypoglycemia

We report three episodes of SH in our study, of which two episodes were seizures with loss of consciousness, and all requiring treatment by emergency room staff. The first participant was in the second trimester and suspended basal insulin for 1 h without resolution of the event and experienced a seizure. The second participant was in the third trimester, ingested oral carbohydrate without resolution of hypoglycemia and had a seizure. The third participant was in the first trimester and had SH due to nausea and vomiting, prohibiting adequate oral intake after a mealtime insulin bolus.

Discussion

In this multicenter prospective observational study, we report hypoglycemia data in pregnancies with pre-existing type 1 diabetes based on the Dexcom G6 CGM. We report CGM-based percentage time in hypoglycemia, hypoglycemic events, and prolonged hypoglycemic events in three time blocks for each 2-week gestational age throughout pregnancy. Our study shows more hypoglycemic events throughout pregnancy and occurred during daytime. However, participants spent higher percentage of time in hypoglycemia and more prolonged hypoglycemia overnight. Our data contribute to the existing literature with analyses of hypoglycemia occurrences by advancing gestation in intervals as frequent as biweekly by presenting biweekly estimates.

Table 2. Biweekly: Hypoglycemic Events Per Participant for Each 2-Week Block During Pregnancy

Hypoglycemic events[a] *per patient*

		24 h		*Overnight (12–6 am)*		*Daytime (6–12 am)*	
Gestational week	N	*Median (IQR)*	P	*Median (IQR)*	P	*Median (IQR)*	P
First trimester							
4–5	3	0 (0, 0.5)	0.09	0 (0, 0)	0.94	0 (0, 0.5)	0.13
6–7	7	1 (0, 2.5)	**<0.001**‡	0 (0, 1)	0.37	1 (0, 1.5)	**<0.001**‡
8–9	8	3 (2, 9)	0.37	0.5 (0, 2.2)	0.69	2 (1, 7.5)	0.39
10–11	11	4 (2.5, 4.5)	0.72	1 (0, 1.5)	0.27	3 (1, 4)	0.28
12–13§	19	4 (1.5, 6)	—	1 (0, 2)	—	3 (1.5, 5)	—
Second trimester							
14–15	24	1.5 (0.8, 9)	0.68	0.5 (0, 2)	0.78	1.5 (0, 5.5)	0.53
16–17	25	4 (2, 7)	0.56	0 (0, 2)	0.86	3 (1, 7)	0.47
18–19	25	3 (0, 6)	0.35	0 (0, 1)	0.34	2 (0, 5)	0.56
20–21	25	3 (1, 4)	**0.04**‡	1 (0, 2)	0.85	1 (0, 3)	**0.01**‡
22–23	25	3 (1, 4)	**<0.001**‡	1 (0, 2)	0.27	1 (0, 4)	**<0.001**‡
24–25	25	2 (1, 5)	**0.01**‡	1 (0, 1)	0.09	1 (0, 4)	**0.02**‡
26–27	25	1 (0, 3)	**<0.001**‡	0 (0, 1)	**0.01**‡	0 (0, 3)	**<0.001**‡
Third trimester							
28–29	25	2 (0, 3)	**<0.001**‡	0 (0, 1)	0.09	1 (0, 2)	**<0.001**‡
30–31	25	3 (0, 5)	**<0.001**‡	1 (0, 2)	0.85	1 (0, 4)	**<0.001**‡
32–33	24	1 (0, 3.2)	**<0.001**‡	0 (0, 1)	0.38	0 (0, 1.2)	**<0.001**‡
34–35	24	2 (0.8, 5)	**0.01**‡	1 (0, 2.2)	0.66	1 (0, 2.2)	**0.01**‡
36–37	20	1 (0, 4.8)	**<0.001**‡	0 (0, 2)	0.48	1 (0, 3)	**<0.001**‡
38–39	12	2 (1, 6.2)	**<0.001**‡	0 (0, 2)	0.07	2 (0.8, 5)	**<0.001**‡

[a]Hypoglycemic events defined as CGM glucose of <54 mg/dL for at least three consecutive measurements (≥15 min) followed by three consecutive readings ≥70 mg/dL.

Results are given as median (IQR) for quantitative data.

N = number of participants biweekly.

Linear mixed-effects model was used to evaluate the statistical significance changes over gestation biweeks in comparison with the reference gestational biweek (12 weeks 0 days to 13 weeks 6 days, indicated by symbol §). Statistical significance threshold of <0.05 is indicated by symbol ‡.

CGM, continuous glucose monitoring.

Prior studies report CGM data for >4-week intervals except for Kristensen et al. who report data in 2-week blocks.[14] Kristensen et al. showed percentage time above goal (>4% as per consensus guidelines)[13] for <63 mg/dL starting around week 9 and stayed above goal throughout pregnancy in rtCGM users in comparison with iCGM users where it started as early as gestational weeks 1 to 4.[14] Participants on rtCGM spent less time below target compared with iCGM users; however, it was still above the recommended consensus percentage (first and second trimester, 7%; third trimester, 6%).

Kristensen et al. report data overall (24 h) throughout pregnancy but did not provide details for distribution of hypoglycemia burden overnight or daytime. Feig et al.[6] and Murphy et al.[24] are two significant studies in the field that report hypoglycemia data along with overall data in pregnancies with type 1 diabetes. However, these studies predate the international consensus guidelines and report data differently. Therefore, we cannot compare our data with these pioneering previous studies. In addition, by using the updated consensus guidelines, we facilitate comparison of our results with future studies that also would probably use the most updated guidelines.

In our study, overnight hypoglycemia (<63 and <54 mg/dL) was present throughout pregnancy with high variability between participants and did not significantly increase or decrease in comparison with reference week. Participants clearly experience more hypoglycemia overnight with high variability in the percentage of hypoglycemia, in particular, this hypoglycemia is more common during the early hours of the overnight period between 12 and 3 am compared with the latter half of the overnight block. This could be related to timing of food intake including bedtime snacks. A second explanation could be need for more frequent overnight basal adjustment than was clinically performed during this observational study.

Hypoglycemic events occurred throughout the pregnancy with median events varying from of one to four events biweekly in the 24-h period in our study. These events decreased significantly for biweeks 18–19 onward compared with the reference biweek. Most hypoglycemic events occurred during daytime compared with the overnight period and decreased significantly for biweeks 18–19 onward as well. Overnight hypoglycemic events were more concentrated during the early hours between 12 and 3 am. During daytime, these events were highly concentrated between 11 and 12, 3 and 8 pm, and at 11 pm. Hypoglycemia between 12 and 3 am could be due to evening meal-related insulin bolus with a potential simultaneous circadian decrease in cortisol levels, leading to increase in insulin sensitivity. During daytime, late morning and afternoon hypoglycemia are likely due to aggressive breakfast and lunch bolus insulin dosing. High insulin sensitivity is seen during the afternoon period

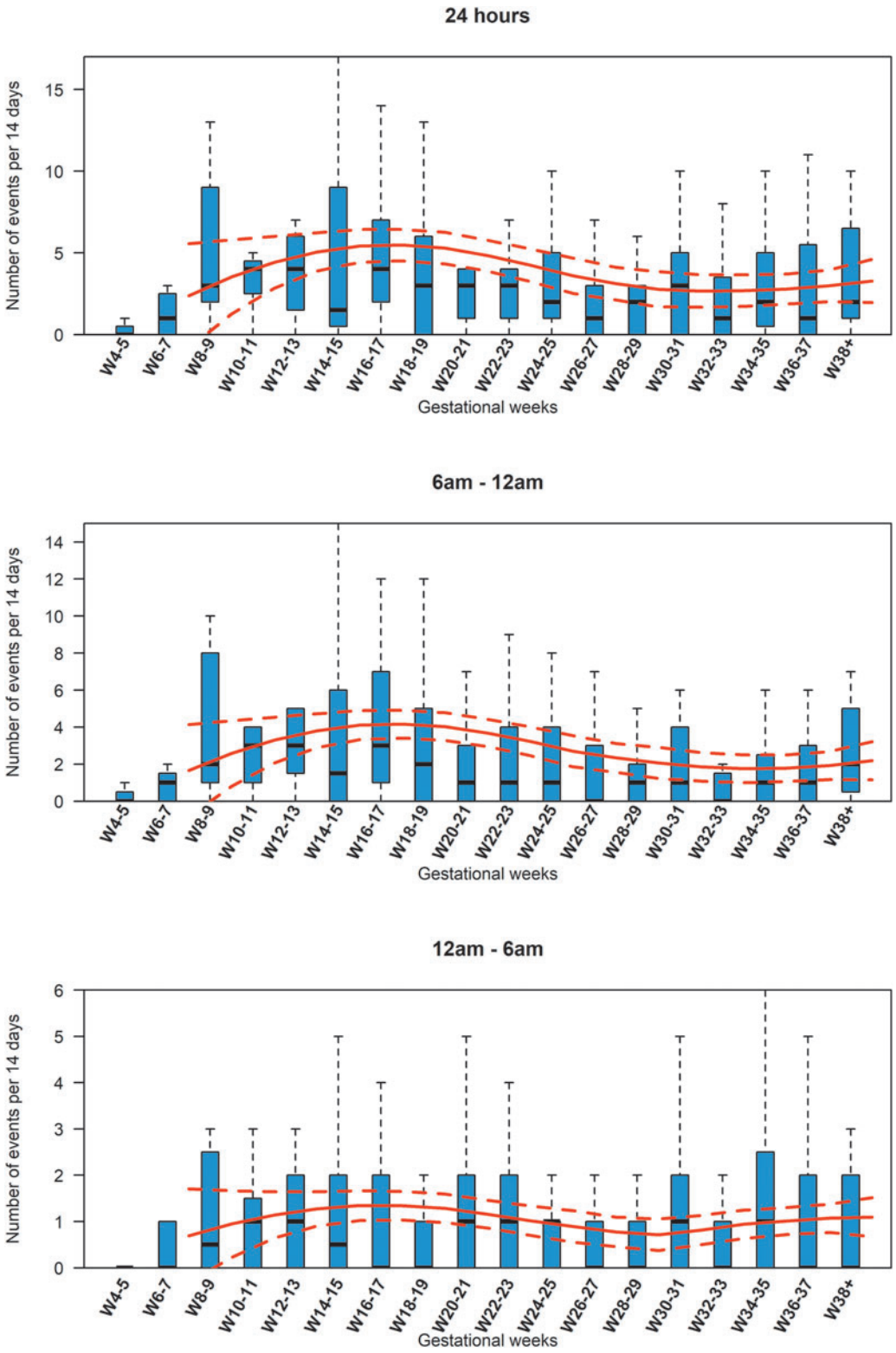

FIG. 3. Median hypoglycemic events (IQR) per patient for each 2-week block (CGM glucose <54 mg/dL for three (≥15 min) consecutive readings) (24 h, 18 h [6–12 am], and 6 h [12–6 am] time blocks). Most hypoglycemic events were observed during daytime (6–12 am) compared with overnight period (12–6 am). LOESS spline (red color) curve goes through the mean. Kindly note the LOESS spline line does not extend all the way left to some of the biweeks. This is because the spline cannot estimate the actual curve with so few patients.

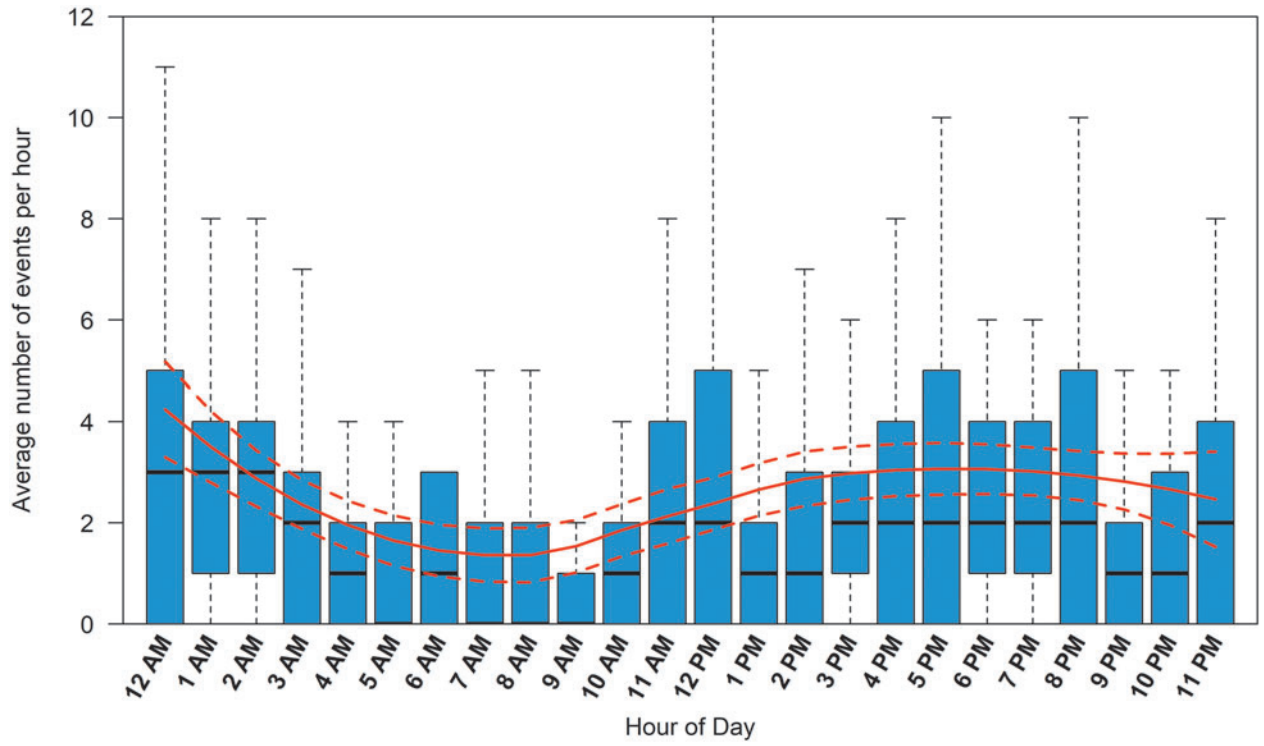

FIG. 4. Frequency of median hypoglycemic events (IQR) by time of day. LOESS spline (red color) curve goes through the mean.

with a possible contribution to this from a decrease in cortisol levels during this time (lowest cortisol concentrations are 1 h after onset of sleep).[25] The exact reason for these episodes would require more analyses of meal carbohydrate and physical activity.

We report prolonged hypoglycemic episodes in this study with maximum prolonged hypoglycemic events occurring during biweeks 18–19 and overnight. To our knowledge, this is the first description of such events in pregnant individuals with type 1 diabetes using the Dexcom G6

Table 3. Biweekly: Number of Prolonged Hypoglycemic Events During Pregnancy

Prolonged hypoglycemic events[a]					
Gestational week	*No. of participants*	*No. of participants who experienced prolonged hypoglycemic events*	*24 h*	*Overnight (12–6 am)*	*Daytime (6 12 am)*
First trimester					
4–5	3	0	0	0	0
6–7	7	0	0	0	0
8–9	8	1	1	1	0
10–11	11	1	1	1	0
12–13	19	0	0	0	0
Second trimester					
14–15	24	0	0	0	0
16–17	25	1	1	1	0
18–19	25	1	2	2	0
20–21	25	0	0	0	0
22–23	25	0	0	0	0
24–25	25	0	0	0	0
26–27	25	0	0	0	0
Third trimester					
28–29	25	1	1	1	0
30–31	25	0	0	0	0
32–33	24	0	0	0	0
34–35	24	0	0	0	0
36–37	20	0	0	0	0
38–39	12	1	1	0	1

[a]Prolonged hypoglycemic events defined as CGM glucose <54 mg/dL for ≥120 min followed by ≥70 mg/dL for 15 min.

sensor. Although we only report confirmed prolonged hypoglycemic events, 61% of the total events were artifactual and appeared to be associated with pressure on the CGM. This highlights the importance of prospective studies to evaluate the optimal site of CGM placement during pregnancy.

Three participants (12%) had clinically SH in our study. Surprisingly, the CGM was not helpful in these instances and could have been impacted by factors that are not able to be clearly elucidated in this observational study. It is not evident that these events are specifically associated with pregnancy-related metabolic changes. Since SH events could happen in any individual with type 1 diabetes who endeavors to achieve tight glucose control, it is not evident that these events are specifically associated with pregnancy related metabolic changes.

Our study has several strengths. With this prospectively collected data set, we report percentage hypoglycemia data per biweek based on the occurrence of a defined hypoglycemic event rather than absolute number of CGM data points in the hypoglycemic range. This is less than overall percentage of time in hypoglycemic range daily eliminating drift of CGM for <15 min into hypoglycemic range. We report hypoglycemic events for each 2-week gestational age block in the cohort using Dexcom G6 CGM, a useful reference for this challenging issue in clinical practice. We report percentage hypoglycemia data per biweek based on the occurrence of a defined hypoglycemic event rather than absolute number of CGM data points in the hypoglycemic range. This is less than the overall percentage of time in hypoglycemic range daily eliminating drift of CGM for <15 min into hypoglycemic range. We report hypoglycemic events for each 2-week gestational age block in the cohort, a useful reference for this challenging issue in clinical practice.

Our study has a few limitations with one being the limited number of enrolled participants. Also, CGM site location varied among participants that may have impacted CGM accuracy, and the site was not routinely available for each 10 days of sensor wear. In addition, it is difficult to unequivocally confirm or exclude CGM data reading in the hypoglycemic range associated with sensor compression. Therefore, variation in CGM glucose value due to positional considerations is an important issue during pregnancy. Also, there was substantially more variability in the percentage under thresholds compared with events; this was due to errant measurements that last a single observation or two observations and contribute to percentage below the threshold but not to events. Furthermore, 95% of our participants were Caucasian race that may limit our ability to generalize these findings to other populations. We acknowledge that mean HbA1c of 6.6% (range: 4.8%–8.9%) is lower than real-world population data. Participants in prospective research studies are generally in better health and may be more adherent than the average patient population. Even with increased adoption of CGM use during pregnancy, hypoglycemia is still a notable concern for clinical care during pregnancies complicated by type 1 diabetes. We did not perform statistical significance testing when we analyzed CGM hypoglycemic events hour by hour since these analyses are exploratory.

The best current therapy in nonpregnant participants to prevent hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL) is closed loop control (CLC).[26,27] Even though CLC systems are approved in the United States, no CLC system is approved for use during pregnancy. A recent randomized controlled crossover trial done by Stewart et al., using CLC for 4 weeks in type 1 diabetes pregnancy, showed a significant decrease in hypoglycemia (<63 mg/dL: 1.6% vs. 2.7% and <50 mg/dL: 0.2% vs.0.5%) and less overnight time <63 mg/dL with CLC compared with SAP therapy.[28] This finding signifies the importance of studying CLC use in pregnancies with type 1 diabetes. Our data further support the urgent need to test the use of CLC systems to reduce the incidence of hypoglycemia in an appropriate size sample of women with type 1 diabetes during pregnancy.

Conclusions

Pregnant women with type 1 diabetes on SAP frequently experience hypoglycemia and hypoglycemic events. Additional research is needed to further evaluate the risks, an ideal location of CGM sites, as well as strategies to reduce hypoglycemia, such as CLC during pregnancies complicated by type 1 diabetes.

LOIS-P Diabetes and Pregnancy Consortium

John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA: Eyal Dassau (PI), Francis J. Doyle III, Basak Ozaslan; Icahn School of Medicine at Mount Sinai, New York: Carol J. Levy (PI), Barak Rosenn (PI), Camilla Levister (I), Grenye O'Malley (I), Dushyanthy Arasaratnam, Emily Nosova, Selassie Ogyaadu; Mayo Clinic, Rochester, MN: Yogish Kudva (PI), Donna Desjardins, Ravinder Jeet Kaur, Walter K Kremers, Corey Reid, Byron Smith, Shelly McCrady-Spitzer, Mari Charisse Trinidad; Sansum Diabetes Research Institute, Santa Barbara, CA: Jordan E. Pinsker (PI), Kristin Castorino (I), Mei Mei Church (I), Jimena Perez, Molly Piper, Camille Andre.

Authors' Contributions

Y.C.K., C.J.L., E.D., J.E.P., B.R., and G.O. helped design the study protocol and ensured the regulatory approval of the study. S.M.S. managed the IRB process. C.R. set up the online platform for data access and management. R.J.K., C.R., S.M.S., B.O., G.O.M., M.C.T., D.D., K.N.C., C.L., S.J.O., M.M.C., M.P., and C.J.L. conducted the study and performed data acquisition. R.J.K, B.H.S., W.K.K., and Y.C.K. analyzed the data and wrote the article. BO provided support in interpretation of the data. R.J.K., B.H.S., J.E.P., B.O., G.O.M., M.C.T., D.D., K.N.C., C.L., C.R., S.M.S., S.J.O., M.M.C., M.P., W.K.K., B.R., F.J.D., C.J.L., E.D., and Y.C.K. edited and reviewed the final article. Y.C.K. is the guarantor of this study, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Disclosure Statement

Y.C.K. is currently a coinvestigator on NIH-funded Artificial Pancreas (AP) studies, has received funding for AP research from JDRF and Helmsley Charitable Trust, has conducted AP research sponsored by Medtronic, and has received research support/product support to his institution

from Tandem Diabetes, Roche Diabetes, and Dexcom Inc.; E.D. reports receiving grants from JDRF, NIH, and Helmsley Charitable Trust, personal fees from Roche and Eli Lilly, patents on artificial pancreas technology, and product support from Dexcom, Insulet, Tandem, and Roche. E.D. is currently an employee and shareholder of Eli Lilly and Company.

The study presented in this article was performed as part of his academic appointment and is independent of his employment with Eli Lilly and Company. J.E.P. is currently an employee and shareholder of Tandem Diabetes Care, Inc. The study presented in this article was performed as part of his academic appointment at Sansum Diabetes Research Institute and is independent of his employment with Tandem Diabetes Care. G.O.M. receives research support from Tandem Diabetes, Insulet, Dexcom, and Abbott paid to her institution.

C.J.L. serves as a coinvestigator on NIH-funded AP studies, has received funding for AP research from JDRF and Helmsley Charitable Trust, and has received research support from Insulet, Abbott Diabetes, Tandem Diabetes, and Dexcom paid to her institution, and has received consulting fees from Dexcom and Eli LIlly. K.C. receives research support provided to her institution from Dexcom, Abbott, Medtronic, and Novo Nordisk. C.M.L. receives research support from Tandem Diabetes, Insulet, Dexcom, and Abbott Diabetes. F.J.D. reports equity, licensed IP, and is a member of the Scientific Advisory Board of Mode AGC. W.K.K. receives research funding from the NIH, DOD, AstraZeneca, Roche, and Biogen all unrelated to this study. No conflicts of interest relevant to this project are reported for the rest of the authors.

Funding Information

Financial support for this study was provided by the National Institutes of Health (Grant No. R01DK120358). Product support was provided by Dexcom, Inc., (AP-2018-016). REDCap data management was supported by the Mayo Foundation Research Computing Facility grant (No. UL1TR002377).

Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5
Supplementary Table S6

References

1. Evers IM, de Valk HW, Mol BW, et al.: Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia 2002;45:1484–1489.
2. Macintosh MC, Fleming KM, Bailey JA, et al.: Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177.
3. Jensen DM, Damm P, Moelsted-Pedersen L, et al.: Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care 2004;27:2819–2823.
4. Murphy HR, Bell R, Cartwright C, et al.: Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. Diabetologia 2017;60:1668–1677.
5. Polsky S, Wu M, Bode BW, et al.: Diabetes technology use among pregnant and nonpregnant women with T1D in the T1D exchange. Diabetes Technol Ther 2018;20:517–523.
6. Feig DS, Donovan LE, Corcoy R, et al.: Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347–2359.
7. Dalfra MG, Sartore G, Di Cianni G, et al.: Glucose variability in diabetic pregnancy. Diabetes Technol Ther 2011;13:853–859.
8. Jovanovic L, Druzin M, Peterson CM: Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. Am J Med 1981;71:921–927.
9. Blumer I, Hadar E, Hadden DR, et al.: Diabetes and pregnancy: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabol 2013;98:4227–4249.
10. Kitzmiller JL, Block JM, Brown FM, et al.: Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care 2008;31:1060–1079.
11. National Institute for Health and Care Excellence: 2020. Diabetes in pregnancy: management from preconception to the postnatal period NICE guideline [NG3] https://www.nice.org.uk/guidance/ng3 (accessed October 20, 2021).
12. The American College of Obstetricians and Gynecologists: 2018. Pregestational Diabetes Mellitus. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/12/pregestational-diabetes-mellitus (accessed October 20, 2021).
13. Battelino T, Danne T, Bergenstal RM, et al.: Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603.
14. Kristensen K, Ögge LE, Sengpiel V, et al.: Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia 2019;62:1143–1153.
15. O'Malley G, Ozaslan B, Levy CJ, et al.: Longitudinal observation of insulin use and glucose sensor metrics in pregnant women with type 1 diabetes using continuous glucose monitors and insulin pumps: the LOIS-P study. Diabetes Technol Ther 2021;23:807–817.
16. Castorino K, Polsky S, O'Malley G, et al.: Performance of the Dexcom G6 continuous glucose monitoring system in pregnant women with diabetes. Diabetes Technol Ther 2020;22:943–947.
17. Danne T, Nimri R, Battelino T, et al.: International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640.
18. Roeder HA, Moore TR, Ramos GA: Insulin pump dosing across gestation in women with well-controlled type 1 diabetes mellitus. Am J Obstet Gynecol 2012;207:324.e1–e5.
19. Mathiesen JM, Secher AL, Ringholm L, et al.: Changes in basal rates and bolus calculator settings in insulin pumps during pregnancy in women with type 1 diabetes. J Matern Fetal Neonatal Med 2014;27:724–728.
20. Garcia-Patterson A, Gich I, Amini SB, et al.: Insulin requirements throughout pregnancy in women with type 1

diabetes mellitus: three changes of direction. Diabetologia 2010;53:446–451.
21. Dunn PK, Smyth GK: Randomized quantile residuals. J Comput Graph Statistics 1996;5:236–244.
22. Gelman A, Hill J: Data analysis using regression and multilevel/hierarchical models. New York: Cambridge University Press, 2006.
23. Brooks ME, Kristensen K, van Benthem KJ, et al.: Modeling zero-inflated count data with glmm TMB. 2017;*bioRxiv* 132753.
24. Murphy HR, Rayman G, Duffield K, et al.: Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care 2007;30:2785–2791.
25. Veldhuis JD, Iranmanesh A, Johnson ML, Lizarralde G: Amplitude, but not frequency, modulation of adrenocorticotropin secretory bursts gives rise to the nyctohemeral rhythm of the corticotropic axis in man. J Clin Endocrinol Metab 1990;71:452–463.
26. Brown SA, Kovatchev BP, Raghinaru D, et al.: Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717.
27. Bergenstal RM, Garg S, Weinzimer SA, et al.: Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408.
28. Stewart ZA, Wilinska ME, Hartnell S, et al.: Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 2018;41:1391–1399.

Address correspondence to:
Yogish C. Kudva, MD
Division of Endocrinology, Diabetes, Metabolism and Nutrition
Mayo Clinic
200 First Street SW
Rochester, MN 55902
USA

E-mail: kudva.yogish@mayo.edu

Carol J. Levy, MD
Division of Endocrinology, Diabetes and Metabolism and Bone Disease
Icahn School of Medicine at Mount Sinai
1 Gustave L. Levy Place, Box 1055
New York, NY 10029
USA

E-mail: levy.carol@mssm.edu