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Baretić, Maja; Lekšić, Gloria; Ivanišević, Marina

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FEATURE ARTICLE



Ambulatory Glucose Profile Changes During Pregnancy in Women With Type 1 Diabetes Using Intermittently Scanned Continuous Glucose Monitoring Empowered by Personalized Education

Maja Baretić, 1,2 Gloria Lekšić, 3 and Marina Ivanišević 2,4

¹Division of Endocrinology and Diabetes, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia; ²University of Zagreb School of Medicine, Zagreb, Croatia; ³Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia; ⁴Department of Gynaecology and Obstetrics, University Hospital Centre Zagreb, Zagreb, Croatia

The ambulatory glucose profile is a valuable tool in managing type 1 diabetes during pregnancy. Time in range (TIR) in the third trimester is one of the most significant parameters contributing to good pregnancy outcomes. This study aimed to evaluate the effect of intermittently scanned continuous glucose monitoring (isCGM) empowered by education on glucose dynamics and to predict third trimester TIR.

Data were retrospectively analyzed from 38 pregnant patients with type 1 diabetes (mean age 30.4 ± 6.4 years, BMI 23.7 ± 3.7 kg/m², disease duration 15.4 ± 9.5 years, preconception A1C $6.9 \pm 1\%$) who used a first-generation Free-Style Libre isCGM system for at least 3 months before conception and had sensor data captured >70% of the time the system was used. Patients received personalized education on diabetes and on minimizing hypoglycemia and hyperglycemia using CGM trend arrows and frequent sensor scanning.

This intervention improved glycemic parameters of glucose regulation (TIR, glucose management indicator, and mean glucose), hyperglycemia (time above range), glucose variability (SD and coefficient of variation [%CV]), and scanning frequency, but did not improve parameters of hypoglycemia (time below range and a number of low glucose events). Logistic regression analysis showed that the first trimester %CV and scanning frequency contributed to the third trimester TIR (P < 0.01, adjusted $R^2 = 0.40$).

This study suggests that the use of isCGM empowered by personalized education improves glycemic control in pregnant women with type 1 diabetes. Scanning frequency and %CV in the first trimester predicts TIR in the third trimester, which could help clinicians intervene early to improve outcomes.

Pregnancy in women with type I diabetes carries a risk for numerous adverse outcomes, including preterm delivery, congenital malformations, preeclampsia, eclampsia, macrosomia, large-for-gestational-age newborn, and neonatal hypoglycemia. Optimal glucose control significantly reduces these outcomes. Current guidelines recommend maintaining an AIC <6.5% (48 mmol/L) throughout pregnancy, if possible without significant hypoglycemia (I). Studies have shown better pregnancy outcomes for women who achieved this target (2). Moreover, AIC in the third trimester has the strongest impact on pregnancy outcomes (3).

Today, continuous glucose monitoring (CGM) makes pregnancy management for women with type I diabetes much

easier. CGM enables continuous 24-hour monitoring of glucose levels in both the fasting and postprandial states. Through CGM, pregnant patients can be aware of their glucose levels at any given time and know when to intervene (e.g., take a correction insulin bolus to reduce hyperglycemia or takes steps to prevent impending hypoglycemia).

Whereas real-time CGM (rtCGM) systems display the sensor glucose values continuously on a monitor (e.g., smartphone, smartwatch, or insulin pump), intermittently scanned CGM (isCGM) systems display the current glucose level and trend only when the sensor is scanned with a handheld reader or smartphone. Unlike rtCGM systems, the first-generation isCGM system does not provide high or low glucose alarms to alert

 $\label{lem:corresponding} \begin{tabular}{ll} Corresponding author: Maja Baretić, maja.baretic@kbc-zagreb.hr https://doi.org/10.2337/ds22-0094 \end{tabular}$

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users to high or low glucose levels. However, is CGM is sometimes the only type of CGM system covered under health insurance policies or is the only one available for pregnant women with type I diabetes.

Although the availability of isCGM is a step forward in type I diabetes management, it is crucial to ensure that patients receive proper education and training on how to use it effectively. Many patients receive only brief instructions or watch an online tutorial video, which may not be sufficient to ensure their full understanding of the CGM system's capabilities and limitations. Unfortunately, many patients do not understand the limitations of this method of glucose monitoring (e.g., the occasionally need to perform fingerstick blood glucose monitoring [BGM] to confirm sensor glucose values) or are not educated about how to interpret and act on the glucose trend arrows the system displays to indicate rising, stable, or declining glucose levels.

Until recently, AIC was the most important marker used to estimate glycemic control. However, CGM enabled the development of new parameters and depictions of glycemia, which are displayed on a standardized ambulatory glucose profile (AGP) report with all CGM systems. The AGP report provides a graphical representation of a person's glucose levels over a period of time. It also provides a summary of CGM-derived metrics. These include time in range (TIR), time below range (TBR), and time above range (TAR), as well as parameters of glucose variability expressed as SD and coefficient of variation (%CV), a glucose management indicator (GMI), which is an estimate of AIC, and an average glucose value over the time period depicted in the report.

The AGP report can be particularly useful for pregnant women with diabetes, as it provides a comprehensive view of glucose levels throughout the day and night. TIR is one of the most used parameters and can replace A_IC as a glycemic marker during pregnancy in women with type I diabetes.

The TIR target is strict during pregnancy. The International Consensus on Time in Range recommends a TIR of 63–140 mg/dL (3.5–7.8 mmol/L) at least >70% of the time in this setting. This target is compared with the recommended TIR target of 70–180 mg/dL (3.9–10.0 mmol/L) for most nonpregnant adults with diabetes (4). Kristensen et al. (5) showed an association between greater TIR and decreased risk for large-for-gestational-age (LGA) newborn. Moreover, a study by Meek et al. (6) analyzed data from 157 pregnant women with type 1 diabetes and showed that TIR and TAR were the CGM metrics most consistently predictive of pregnancy outcomes. A study by Scott et al. (7) showed that women delivering newborns of normal-for-gestational-age weight

had significantly higher first-semester TIR than those delivering LGA newborns (55 vs. 50%).

The CONCEPTT study (8) compared the use of rtCGM to BGM and confirmed the positive impact of CGM technology on pregnancy in women with type I diabetes. The study pointed out that an increase of just 7% in TIR yielded benefit on pregnancy outcomes. To date, no clear data have shown that is CGM affords the same benefits in this population. However, the use of isCGM has increased because it is a cheaper and more accessible alternative for some people with type I diabetes. Some studies found that isCGM used during pregnancy in women with type I diabetes provided an initial improvement in glycemic control that was not sustained (9), and others found out that mean sensor glucose was similar when measured by isCGM and rtCGM (10). Recent data revealed that the combination of isCGM and personalized education significantly reduced TBR in nonpregnant patients with type I diabetes (11,12).

This study aimed to assess the dynamics of the AGP during pregnancy in patients with type I diabetes who used an isCGM system and had personalized education on diabetes management and isCGM usage. An additional aim was to predict third-trimester TIR, the CGM-derived metric most closely associated with pregnancy outcomes, based on first-trimester CGM parameters.

Research Design and Methods

We performed a retrospective cohort study of pregnant women with type I diabetes who were followed at the University Hospital Centre Zagreb (State Reference Centre for Treatment of Diabetes in Pregnancy) from January to November 2021. Inclusion criteria were a diagnosis of type I diabetes for at least 2 years before pregnancy, enrollment in the study during the first trimester of pregnancy, is CGM use for a minimum of 3 months before conception, receipt of personalized education, and glucose data availability >70% of time is CGM was used. All of the participants were treated with multiple daily injections using insulin analogs.

All of the patients were followed by experienced diabetologists and gynecologists monthly in a setting offering inpatient and outpatient care. At every visit, endocrinologists also educated patients about the benefits of strict glucose control during pregnancy and the use of isCGM.

There was no specific education curriculum; patients received personalized education based on their isCGM glucose data during the previous month. The approach to individual sessions varied depending on previous data analysis and patients' backgrounds and overall knowledge of the disease.

Some patients received re-education regarding general diabetes knowledge. The main purpose of the education was to anticipate future glucose dynamics and to be proactive in controlling glycemia during pregnancy. The education covered prandial insulin dose adjustments, as well as changes in the insulin-to-carbohydrate ratio and insulin sensitivity factor throughout the three trimesters. Patients were also instructed regarding the use of isCGM and how to prevent hypoglycemia and hyperglycemia by interpreting isCGM glycemic trend arrows and scanning the sensor frequently (≥10 times a day). They were also instructed on how to plan the carbohydrate content of meals, plan future physical activities, and use trend arrows indicating glucose dynamics and insulin demands adjusted to each trimester of pregnancy. For example, if patients predicted hypoglycemia based on the information provided by isCGM, they were instructed to perform a BGM check and eventually to ingest carbohydrates. If they predicted hyperglycemia, they were instructed to scan their sensor again in 15 minutes and add a correction dose of prandial insulin.

Retrospectively analyzed records included the following data from patients' medical history: age at type I diabetes diagnosis, age at the time of conception, BMI at the time of conception, and laboratory measured AIC in the preconception period. The following isCGM data were analyzed for every pregnancy trimester: TIR, TBR, TAR, number of low glucose events, time spent with very high glucose defined as >250 mg/dL (13.9 mmol/L), time spent with very low glucose defined as <54 mg/dL (3.0 mmol/L), scanning frequency, mean sensor glucose, and GMI. GMI is a metric estimating the A_IC level that would be expected based on CGM-derived glucose values. It was calculated using the formula GMI (%) = $3.31 + 0.02392 \times [\text{mean glu-}]$ cose in mg/dL] or GMI (mmol/mol) = $12.71 + 4.70587 \times [mean]$ glucose in mmol/L]. We also included parameters of glucose variability, including SD and %CV. %CV is the ratio of the SD to the mean glucose. It shows the level of dispersion around the mean, expressed as a percentage.

Participants used a first-generation FreeStyle Libre isCGM system with each sensor measuring interstitial glucose levels for 2 weeks without the need for calibration. The handheld system reader was used to scan the sensor, and each scan was recorded to enable determination of scanning frequency. The system reader collected and displayed the glucose data (current glucose level, glucose trend arrow, and the most recent 8-hour history of glucose levels), and the stored glycemic data were uploaded by physicians during visits using the complementary software (LibreView, Abbott Diabetes Care) (13). The target glucose range of 63–140 mg/dL (3.5–7.8 mmol/L) was set according to recommendations from the International Consensus on Time in Range for pregnancy in people with diabetes (4).

Statistical analyses were performed using SPSS Statistics, v. 24.0 (IBM Corp.), with the level of statistical significance set at P < 0.05. The numerical data were presented as means and SDs, and categorical data were presented as percentages. Differences in isCGM parameters between trimesters were assessed using paired samples t tests. Associations of CGM parameters were evaluated by stepwise linear regression analysis.

Results

A total of 38 pregnant patients with type I diabetes were included in the study. The basic characteristics of the cohort were as follows: age 30.4 \pm 6.4 years, BMI 23.7 \pm 3.7 kg/m², type I diabetes duration 15.4 \pm 9.5 years, and preconception AIC 6.9 \pm 1.1%. The incidence of LGA was 37.4%, and the average week of delivery was 37 \pm 2 weeks' gestation. A total of 15 patients were excluded from the analysis because they had <70% of CGM data available during follow-up and/or were not able to attend monthly visits.

Most of the isCGM-derived glycemic parameters showed significant improvement throughout pregnancy (Table 1). There was a statistically significant increase in TIR from the first to third, first to second, and second to third trimesters and a statistically significant increase in scanning frequency from the first to third and first to second trimesters. There was statistically significant decreases in TAR, time spent in the very high glucose range, SD, %CV, and GMI from the first to third and first to second trimesters and in mean glucose from the first to third, first to second, and second to third trimesters.

This cohort had a high incidence of hypoglycemia, as seen in the levels of TBR, time spent with very low glucose, and a number of low glucose events. There was no statistically significant difference in variables describing hypoglycemia between the first and third trimesters, but there was a difference between the first and second and second and third trimesters.

Regarding the prediction of third-trimester TIR, logistic regression analysis showed that first-trimester %CV and scanning frequency were variables contributing to third-trimester TIR (P < 0.01, adjusted R^2 0.40).

Discussion

In this cohort study, we retrospectively analyzed data from pregnant women with well-controlled type I diabetes and evaluated the improvement in glycemic parameters from the AGP report while using isCGM empowered by personalized education. Patients (mean age 30 years and mean diabetes duration 15 years) had frequent visits, which included education

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TABLE 1 CGM Variables During First, Second, and Third Trimesters of Pregnancy						
CGM Variables	First Trimester, mean ± SD	Second Trimester, mean ± SD	Third Trimester, mean ± SD	First to Third Trimester P	First to Second Trimester P	Second to Third Trimester P
Scanning frequency, n	10.32 ± 6.70	13.66 ± 8.67	16.36 ± 7.65	< 0.01	0.01	0.11
Mean sensor glucose, mg/dL (mmol/L)	127.93 ± 24.32 (7.10 ± 1.35)	108.50 ± 96.58 (6.02 ± 5.36)	111.17 ± 87.57 (6.17 ± 4.86)	< 0.01	< 0.01	0.01
TIR: 63-140 mg/dL (3.5-7.8 mmol/L), %	54.65 ± 12.14	62.58 ± 8.22	67.03 ± 9.38	< 0.01	< 0.01	0.01
TAR: >140 mg/dL (7.8 mmol/L), %	34.38 ± 16.00	21.55 ± 11.45	21.87 ± 12.70	< 0.01	< 0.01	0.10
Very high glucose: >250 mg/dL (13.9 mmol/L), %	4.32 ± 5.77	0.77 ± 0.52	0.625 ± 0.40	< 0.01	< 0.01	0.67
TBR: >63 mg/dL (3.5 mmol/L), %	11.16 ± 8.14	15.86 ± 9.54	11.09 ± 9.35	0.81	< 0.01	< 0.01
Very low glucose: <54 mg/dL (3.0 mmol/L), %	5.96 ± 5.45	8.34 ± 5.94	5.16 ± 5.35	0.61	0.03	< 0.01
Low glucose events, n	107.32 ± 70.42	151.21 ± 78.23	115.03 ± 73.81	0.06	< 0.01	< 0.01
%CV	41.92 ± 6.80	39.09 ± 5.44	34.67 ± 6.04	< 0.01	0.02	< 0.01
SD, mg/dL (mmol/L)	59.28 ± 33.51 (3.29 ± 1.86)	41.44 ± 40.90 (2.30 ± 2.27)	40.54 ± 51.89 (2.25 ± 2.88)	< 0.01	0.01	0.92
GMI, %	6.39 ± 5.81	5.89 ± 4.05	5.93 ± 4.34	< 0.01	< 0.01	0.08

regarding the benefits of strict glucose control, carbohydrate counting, and adjustment of prandial insulin doses through the trimesters, as well as the use of isCGM. This combination of technology use and a personalized approach resulted in a significant increase in TIR in the third trimester of pregnancy, as well as decreases in parameters of hyperglycemia (TAR and time spent with very high glucose), glucose variability (SD and %CV), and glucose regulation (GMI and mean glucose).

Why is TIR during the third trimester important? It is well known that optimal glucose regulation during pregnancy significantly decreases the risks for adverse pregnancy outcomes such as preeclampsia, eclampsia, perinatal mortality, congenital anomalies, neonatal hypoglycemia, LGA infant, and macrosomia. Lower AIC during all trimesters of pregnancy is associated with decreased rates of LGA, and the strongest association is with third-trimester AIC. Today, AIC is mostly being replaced by CGM-derived metrics to assess glycemic management (12).

In our study, TIR was 55% in the first trimester, increasing to up to 67% (almost within the target range) in the third trimester. Still, there remains a question regarding whether intervention should be done in the preconception period to reach optimal TIR as early as possible during pregnancy and thereby improve obstetric and neonatal outcomes. In our cohort of patients, GMI improved throughout pregnancy (from 6.39% in the first trimester to 5.93% in the third trimester), and average glucose improved from 127.8 mg/dL (7.1 mmol/L) in the first trimester to III.06 mg/dL (6.17 mmol/L) in the third trimester. We noticed a statistically significant decrease in parameters of

hyperglycemia (TAR and time spent in the very high glucose range) but not in variables of hypoglycemia.

Our results align with data from the previously mentioned study by Meek et al. (6), which did not find TBR to be a predictive CGM metric for pregnancy outcomes. This does not mean that the risk of hypoglycemia should be underestimated; indeed, severe hypoglycemia occurs in up to half of pregnancies in women with type I diabetes, mostly in the first trimester (I4,I5).

This cohort of patients had a high percentage of TBR (II% in the third trimester) and time in a very low range (5% in the third trimester), and such results may represent a disadvantage of first-general isCGM compared with rtCGM. Although the high and low glucose alarms available with rtCGM and later-generation isCGM systems can be frustrating, pregnant patients with type I diabetes who used rtCGM appeared to have less TBR at all gestational ages (II). Second-generation is CGM may be an affordable option to better enable the prevention of hypoglycemia. This more recent iteration of isCGM technology incorporates Bluetooth connectivity to a mobile smartphone app and offers optional alarms for both hypoglycemia and hyperglycemia. We recommend using such a mobile app for pregnant patients who are not meeting International Consensus TBR targets (time <63 mg/dL [3.5 mmol/L] <4% and time <54 mg/dL [3.0 mmol/L] < 1%) (4).

We assume that the education provided to study participants improved outcomes by engaging participants more in diabetes self-management. isCGM scanning frequency is an interesting variable that can offer insight into patients' engagement in the process of glucose control that is unavailable when using rtCGM. For pregnant patients with type I diabetes, the aim is to have a higher number of daily scans, given that increased glucose monitoring in all patients with type I diabetes is associated with better glycemic control (16). Scanning frequency in our cohort increased significantly from a surprisingly low 10 per day in the first trimester to 16 per day in the third trimester. In a recent study by Canecki Varzic et al. (17). involving 425 patients with type I diabetes in Croatia, the average number of scans per day was 17, which is much higher than in our cohort. Compared with the worldwide database (13) scans per day), the overall average number of scans per day in Croatia is high, but compared with the Polish database (21 scans per day), it is low (18). There is no clear consensus on an optimal number of scans per day for subpopulations of patients such as pregnant patients with type I diabetes. Again, the preconception period could be an ideal time to point to the necessity of greater self-management engagement as expressed as a higher number of daily scans.

A search for new markers of pregnancy outcomes in type I diabetes is ongoing, and glucose variability is one possibility. In our cohort, variables of glucose variability significantly decreased from the first to the third trimesters (SD from 55.28 to 40.54 mg/dL [from 3.29 to 2.25 mmol/L] and %CV from 4I.92 to 34.67%). Some studies have found that glucose variability measures have an impact on type I diabetes pregnancy outcomes (19,20), whereas others have found no effect (2I). The issue remains controversial, and larger prospective studies are needed to confirm an association between glucose variability and pregnancy outcomes in type I diabetes. Because low glucose variability is a consequence of both less hypoglycemia and less hyperglycemia, it would be expected to influence pregnancy outcomes in some way.

This study showed that variables from the first trimester (specifically %CV and scanning frequency) predict third-trimester TIR. This means that patients who do not scan frequently and have high glucose variability in the first trimester are more likely to have lower TIR in the third trimester. Scanning frequency shows that the patient is actively involved in decisions regarding her glucose management. In patients with type I diabetes (not only pregnant ones), higher scanning frequency results in better glycemic control and greater TIR (22). In pregnancy, it is important to identify patients at risk for poor glycemic control as early as possible in the first trimester. Improving parameters from early pregnancy that contribute to

the third-trimester TIR could help to improve glucose regulation throughout pregnancy.

Limitations

The limitations of this study include the small sample size of patients with good glycemic regulation in the preconception period and high isCGM usage who were recruited from a specialized medical center. Also, the retrospective study design could result in missed anamnestic data throughout pregnancy that could have influenced glycemic control. However, strengths of this study are that it is the first in Croatia to our knowledge that analyzed the use of isCGM empowered with individualized education during pregnancy in women with type I diabetes and that it evaluated parameters as possible prognostic markers for patients at risk for poor glycemic control in the third trimester and therefore higher risk for adverse outcomes.

Conclusion

In this study, we analyzed the AGP report data of pregnant patients with type I diabetes and found that the use of isCGM together with personalized education resulted in improved glycemic control. Throughout pregnancy, improvements were seen in parameters related to glucose regulation, hyperglycemia, and glucose variability, but not hypoglycemia. For patients who experienced more hypoglycemia, using a newer-generation isCGM that has a smartphone app and can provide low glucose notifications could help to reduce both the amount of time spent with very low glucose and the number of low glucose events.

We also found that some first-trimester parameters (low scanning frequency and high %CV) are prognostic factors for poor glycemic control (lower TIR) later in pregnancy. This finding suggests that regular monitoring of glucose levels using isCGM (i.e., scanning frequency as a marker of self-management engagement) along with appropriate education and management can help to improve glycemic control during pregnancy. Starting isCGM and education earlier, even before conception, may further enhance glycemic control during pregnancy. Monitoring certain parameters such as %CV and scanning frequency in the first trimester can predict TIR in the third trimester, which could help clinicians recognize patients at risk for poor glycemic control and possibly make early interventions to improve pregnancy outcomes.

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FEATURE ARTICLE CGM Use During Pregnancy in Type 1 Diabetes

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

M.B. drafted the article. G.L. performed the statistical analysis and collected data. M.I. collected data. M.B. is the guarantor of this work and, 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.

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