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Real-world data on the Minimed 780G advanced hybrid closed-loop system use during type 1 diabetes pregnancy: One centre observational study

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ABSTRACT

Aim

The efficacy of hybrid closed-loop systems (HCLs) in managing glycemic control in pregnant women with type 1 diabetes remains inadequately characterized. We evaluated the use of the Medtronic Minimed 780G HCLs.

Methods: The retrospective observational study analyzed the glycemic and perinatal outcomes of pregnant women using the HCLs, followed at our tertiary centre. Independent *t*-tests were employed to compare data among trimesters based on pre-pregnancy HbA_{1c}. The associations between glycemic parameters and perinatal outcomes were explored using Spearman rho.

Results: Among the 21 women (age: 33.5 ± 4.2 years, diabetes duration: 21.2 ± 7.6 years, pre-pregnancy HbA_{1c} 7.0 ± 1.1 % (52.9 ± 11.9 mmol/mol)) time in range (pTIR, 63–140 mg/dl; 3.5–7.8 mmol/l) increased progressively throughout pregnancy (trimesters: first: 64.0 ± 9.0 %; second:71.3 ± 11.8 %; third: 75.7 ± 8.1 %). Simultaneously, mean sensor glucose decreased (trimesters: first: 130 ± 10.4 mg/dl (7.2 ± 0.6 mmol/l); second: 120.9 ± 13.4 mg/dl (6.7 ± 0.7 mmol/l); third: 117.3 ± 9.1 mg/dl (6.5 ± 0.5 mmol/l)). Although a majority of women achieved the target pTIR until the third trimester, this did not consistently prevent the delivery of a large-for-gestational-age baby. Notably, one ketoacidosis event occurred, and there were no reported instances of severe hypoglycemia.

Conclusion: Use of the Minimed 780G HCLs enabled the attainment of recommended pregnancy glycemic targets for most women with type 1 diabetes in a real-world setting.

1. Introduction

Living with type 1 diabetes during pregnancy poses a particular challenge. Hormonal changes introduce increased variability in insulin sensitivity, leading to delayed postmeal glucose uptake and insulin absorption, especially in late pregnancy.[1] Notably, in a study-setting, despite using continuous glucose monitoring, only 61–68 % of women reach the target time (>70 %) within the recommended pregnancy target glucose range (pTIR; 63–140 mg/dl (3.5–7.8 mmol/l)), and this achievement is typically observed only in the late third trimester, possibly too late for preventing accelerated fetal growth.[2,3]

New automated algorithm-controlled insulin delivery systems, utilizing real-time continuous glucose monitoring (CGM) and also known as hybrid closed loop systems (HCLs), have revolutionized care for individuals with type 1 diabetes. These systems have shown a 5–10 % improvement in time in range (TIR) across studies compared to conventional pump therapy.[4,5] Despite their proven efficacy in non-pregnant individuals with type 1 diabetes, except for CamAPS, these systems are currently not licensed for use during pregnancy. However, the first randomized controlled trial involving the CamAPS system recently confirmed its safety and its association with improved glycemic control compared to standard intensive insulin therapy in pregnancy.[6]

The Medtronic Minimed 780G is a commercially available HCL system, that automatically adapts insulin basal rates and delivers automated hyperglycemia correction boluses. While the automatic algorithm (SmartGuard) was not initially designed for pregnancy, its ability to set the target glucose at 100 mg/dl (5.5 mmol/l) and its user-friendly algorithm make it a promising tool for glycemic control during pregnancy. Our previous study with a small cohort of six women, comparing sensor-augmented pump therapy in the first pregnancy and the Minimed 780G HCLs in the second, demonstrated that women spent more time in the pTIR (reaching on average 84 % TIR in the third trimester), less time

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above the target range (pTAR), and had lower glucose variability with the Minimed 780G HCLs.[7] In addition, a recently published randomized controlled study examining the safety and clinical efficacy of the Minimed 780 HCLs during pregnancy showed improved overnight pTIR, reduced pTBR and improved treatment satisfaction with this system compared to multiple daily insulin injections or insulin pump therapy with any type of CGM.[8] In the present study, we aimed to analyze the efficacy of achieving glycemic goals with the use of the commercially available HCLs Minimed 780G during type 1 diabetes pregnancy in a real-world setting. Additionally, we aimed to conduct a comprehensive descriptive analysis investigating the intricate association between glycemic targets established during each trimester of pregnancy and their associations with perinatal outcomes.

2. Materials and methods

This retrospective observational study utilized clinical data abstracted from medical records of pregnant women with type 1 diabetes who received care at the pregnancy outpatient clinic of the Department of Endocrinology, Diabetes and Metabolic Diseases at the University Medical Center Ljubljana, Slovenia, including data from 6 women, with some of their data published previously.[7] Following positive experiences since the launch of the Minimed 780G Medtronic HCLs in Slovenia in 2021 outside pregnancy, we initially offered it to a pregnant woman with hypoglycemia unawareness and a history of severe hypoglycemia from her previous pregnancy. Subsequently, based on positive outcomes observed during this pregnancy, we extended the offer of its use to all pregnant women with type 1 diabetes already using any insulin pump therapy and continuous glucose monitoring, irrespective of their clinical characteristics. No other inclusion or exclusion criteria were applied. Slovenian Health Insurance Institute covered the costs of the system during pregnancy.

All participants provided informed consent for treatment with the HCLs during pregnancy. The Minimed 780G pump system integrates an insulin pump, CGM data, and a control algorithm to dynamically adjust insulin infusion with the option of autocorrection bolus. Women who started with Minimed 780G system during pregnancy first spent one week in the manual mode with the same settings of basal insulin and insulin-to-carb ratio as were used with their previous insulin pump. After one week, they switched to automode. Women who already used Minimed 780G system before pregnancy, continued in automode throughout the pregnancy. Target glucose rates were uniformly set at 100 mg/dl (5.5 mmol/l), the lowest of the pre-set options, and active insulin time at 2 h. As a hybrid closed-loop system, manual meal boluses of insulin were delivered based on carbohydrate counting. All women underwent an educational update on carbohydrate counting and the specifics of diabetes self-management during pregnancy at the beginning of the pregnancy. Additionally, women initiating the HCLs during pregnancy received education on the technical aspects of system use. They were advised about the adjustments necessary to ensure proper postprandial glucose control by modifying carbohydrate-to-insulin ratios and by "assisted carbohydrate estimation" (presenting more carbohydrates to the system than actually consumed) when hyperglycemia was corrected too slowly and glucose increased above 145 mg/dl (8.0 mmol/l), especially during the early morning hours in the advanced pregnancy, when the automatic algorithm could not always keep up with the increasing insulin needs due to progressive increase in insulin resistance. An emphasis was on proper pre-meal bolus timing according to the pregnancy stage (insulin application 30–45 min before meals in late gestation), dietary intake of carbohydrates, evenly distributed throughout the day, avoidance of hypoglycemia overcorrection and on regular physical activity immediately after the main meals.[9,10]

All women received specialist antenatal care from a multidisciplinary team, including gynecologists, endocrinologists, nurse educators, ophthalmologists, dieticians, and psychologists. Visits at our pregnancy diabetes clinic were scheduled every 2 to 4 weeks. Parameters recorded at each visit included weight, blood pressure, insulin dose, adverse events, any episodes of severe hypoglycemia and HbA_{1c} measurements. Women were carefully monitored for the recommended weight gain and blood pressure at each visit during pregnancy. They also had urinary exams performed at every visit to monitor possible proteinuria or urinary tract infection. Gynecologists evaluated the risk for preeclampsia and instituted therapy with acetylsalicylic acid, as appropriate. Additionally, glycemic data were regularly reviewed online by the expert for diabetes management during pregnancy on a weekly basis. Suggestions about how to improve glycemic management were then sent to women via e-mail or telephone call.

Data on concomitant diseases and chronic diabetes complications were obtained from medical records at the first prenatal visit. Diabetic nephropathy was defined based on persistent albuminuria, with urinary albumin-creatinine ratio $\geq$ 30 mg/g at least on two occasions or estimated glomerular filtration rate below 60 ml/min/1.73m^2[11] within the year before the first prenatal visit. Based on the ophthalmologist's exam, individuals with mild to moderate non-proliferative diabetic retinopathy were defined as having non-proliferative diabetic retinopathy. Individuals with severe non-proliferative or proliferative diabetic retinopathy were classified into the pre-proliferative/proliferative diabetic retinopathy group. Gestational hypertension was defined as blood pressure greater than or equal to 140 mmHg systolic or 90 mmHg diastolic on two separate occasions at least 4 h apart after 20 weeks of pregnancy when previous blood pressure was normal. Excessive gestational weight gain (GWG) was defined as weight gain greater than that recommended by the Institute of Medicine guidelines.[12] Severe hypoglycemia was defined as a state of an altered mental and/or physical functioning that requires assistance from another person for recovery from hypoglycemia. Impaired hypoglycemia awareness was defined as a lack of experiencing the typical counter regulatory hormone release at low glucose levels or the associated symptoms. Diabetic ketoacidosis was characterized by positive urinary or serum ketones and evidence of metabolic acidosis with a venous blood pH <7.30 and/or bicarbonate <15 mmol/l. Pre-conception HbA_{1c} was calculated as an average HbA_{1c} value during the last 5 visits before pregnancy, if available; otherwise, the last HbA_{1c} before pregnancy was used. Pre-specified pregnancy outcome parameters were collected from the electronic records of the Division of Gynecology and Obstetrics of the University Medical Centre Ljubljana, Slovenia. These parameters included miscarriage (<22 weeks of gestation), large for gestational age (LGA) infant (birth weight $\geq$ 90th percentile, using locally derived standardized centiles,[13] adjusted for gestational age and sex), appropriate for gestational age (AGA) infant (birthweight between 10th and 90th percentile), small for gestational age (SGA) infant (birth weight < 10th percentile, using locally derived standardized centiles,[13] adjusted for gestational age and sex), preterm delivery (<37 weeks of gestation), birth trauma, neonatal hypoglycemia (2-h plasma glucose concentration < 45 mg/dl (<2.5 mmol/l)), neonatal jaundice, treated with phototherapy, neonatal death and stillbirth.

The study adhered to the guidelines of the Declaration of Helsinki and Good Clinical Practice. It was approved by the Slovenian Ethics Committee (number 0120–61/2023/3).

2.1. Statistical analyses

The study encompassed all women who used Minimed 780G HCLs during pregnancy and gave birth before the manuscript preparation; hence, we did not calculate a specific sample size needed.

CGM data were analyzed from the raw glucose data separately for each trimester, constituting a span of 90 days per trimester. We assessed the mean CGM glucose concentration, coefficient of variation, glucose management indicator (GMI), and percentage of time spent in the target glucose range (pTIR). The target glucose range was defined as a concentration of 63–140 mg/dl (3.5–7.8 mmol/l). Additionally, we calculated the time spent below glucose concentration 63 mg/dl (3.5 mmol/l) (pTBR) and above glucose concentration 140 mg/dl (7.8 mmol/l)

(pTAR) over the 24-h period, as well as separately during the night-time and during day-time. GMI is a metrics that approximates the expected laboratory HbA_{1c} level based on average glucose measured using CGM values.[14] Furthermore, we recorded data on carbohydrate intake, insulin dose, changes in carb-to-insulin ratio, the need for autocorrection, and basal insulin dose during advancement of pregnancy.

Data analysis was conducted using SPSS Statistics version 28 (IBM, Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria. The assessment of variable distribution was performed using the Shapiro-Wilk test. Descriptive statistics for normally distributed data were presented as mean with the corresponding standard deviation, while variables that deviated from normal distribution were presented as median with interquartile ranks. Glycemic outcomes in women achieving target HbA_{1c} pre-pregnancy (≤6.5 % (48 mmol/mol))[15] were compared to glycemic outcomes in women with HbA_{1c} above the target range using an independent samples *t*-test. Associations between variables were examined using the Spearman rho correlation coefficient. The receiver operating curve (ROC) was utilized to demonstrate the performance of each trimester's mean sensor glucose concentration to predict the birth of a LGA baby.

Glycemic parameters for the first trimester were exclusively presented for the 14 women using the Minimed 780G during the first trimester. Those utilizing different systems were excluded from this specific analysis, as the focus was on demonstrating the effectiveness of the closed-loop system. However, the entire sample was considered in the analysis of the association between glycemic parameters and perinatal outcomes. There were no other missing values.

3. Results

This study comprised a cohort of 21 consecutive women (average age: 33 ± 4.2 years) with type 1 diabetes (diabetes duration: 20.2 ± 7.4 years) treated with insulin pumps and CGM before pregnancy and received treatment at our tertiary centre. Upon receiving information about the study, all women except one agreed to undergo treatment using Minimed 780G HCLs. Among them, nine women were already using this system before considering pregnancy and then continued with it during pregnancy, while the remaining twelve switched to the HCLs after first visit at diabetes clinic during pregnancy until up to the 14th gestational week. The observational period from the first visit of the first woman included up to the delivery of the last woman included was 21 months.

All women included were Caucasian with singleton pregnancies. The average participant's pre-pregnancy body mass index (BMI) was 25.2 ± 4.4 kg/m^2. During pregnancy, the average GWG was 11 ± 5.6 kg. Before pregnancy, 9 out of 21 women had HbA1c ≤6.5 % (48 mmol/mol). Eleven women (52 %) performed a pre-pregnancy visit at diabetes pregnancy clinic and received treatment with folic acid preconceptionally. Non-proliferative diabetic retinopathy was observed in 13 (61.9 %) women, while 3 (14.3 %) had pre−/proliferative retinopathy. None of the participants had established kidney disease. Clinical characteristics of women included are detailed in Table 1.

3.1. Glycemic control across gestation

An average target pre-conceptional HbA_{1c} of 6.5 % (48 mmol/mol) or less was achieved by 9 women (43 %); ranging from 5.7 % to 10.1 % (70.7–158.4 mmol/mol). The group with higher pre-pregnancy HbA_{1c} was numerically younger, achieved lower level of education, was more likely nulliparous and was more likely using the Minimed HCLs preconceptionally. Due to the small number of participants, "*p* values" were not calculated.

Throughout pregnancy, the average target HbA_{1c} was achieved by 16 (76.2 %) women in the first, 20 (95.2 %) in the second, and 20 (95.2 %) in the third trimester, respectively.

The median percentage of time participants used the closed-loop system remained consistently high, at 98 %, throughout pregnancy. The mean (±SD) percentage of time that maternal glucose levels were within the pregnancy-specific target range increased across trimesters, from 64.0 ± 9.0 %, to 71.3 ± 11.8 % and 75.7 ± 8.1 % in the first,

Table 1
Clinical characteristics of women included.

	Total sample	Pre-pregnancy HbA1c ≤ 6.5	Pre-pregnancy HbA1c > 6.5
	Mean ± SD		
Age, years	33.5 ± 4.2	35.0 ± 3.9	32.3 ± 4.2
Education			
Intermediate, n (%)	6 (28.6)	1 (11.1)	5 (41.7)
Advanced, n (%)	15 (71.4)	8 (88.9)	7 (58.3)
Diabetes duration, years	20.2 ± 7.4	21.0 ± 8.8	19.6 ± 6.6
< 10 years	3 (14.3)	2 (22.2)	1 (8.3)
10–19 years	5 (23.8)	1 (11.1)	4 (33.3)
> 20 years	13 (61.9)	6 (66.7)	7 (58.3)
Parity			
Nulliparous, n (%)	8 (38.1)	2 (22.2)	6 (50.0)
Multiparous, n (%)	13 (61.9)	7 (77.8)	6 (50.0)
Pre-conception BMI, kg/m^2	25.2 ± 4.4	24.0 ± 3.7	26.2 ± 4.9
Pre-conception HbA_{1c}			
%	7.0. ± 1.1	6.1 ± 0.3	7.6 ± 1.0
mmol/mol	52.9 ± 11.9	43.4 ± 3.8	60.1 ± 7.2
GWG, kg	11.0 ± 5.6	10.6 ± 2.6	11.3 ± 7.2
Insufficient GWG[a]	6 (28.6)	2 (22.2)	4 (33.3)
Recommended GWG	11 (52.4)	7 (77.8)	4 (33.3)
Excessive GWG	4 (19.0)	0 (0)	4 (33.3)
Vomiting during pregnancy, n (%)	1 (4.8)	0 (0)	1 (8.3)
Smoking, n (%)	2 (9.5)	0 (0)	2 (16.7)
Insulin			
Aspart, n (%)	11 (52.4)		
Fast-acting aspart, n (%)	6 (28.6)		
Lispro, n (%)	2 (9.5)		
Pump used before pregnancy			
Minimed Paradigm Veo, n (%)	2 (9.1)	1 (11.1)	1 (8.3)
Minimed 640G, n (%)	6 (28.6)	5 (55.6)	1 (8.3)
Minimed 670G, n (%)	1 (4.8)	0 (0.0)	1 (8.3)
AccuCheck Combo, n (%)	3 (14.3)	3 (33.3)	0 (0.0)
Minimed 780G, n (%)	9 (42.9)	0 (0.0)	9 (75)
Concomitant disease			
Celiac disease, n (%)	1 (4.8)		
Chronic hypertension, n (%)	0 (0)		
Gestational hypertension, n (%)	1 (4.8)		
Hashimoto thyroiditis, n (%)	4 (19.0)		
Retinopathy, non-proliferative, n (%)	13 (61.9)		
Retinopathy, pre-proliferative/proliferative, n (%)	3 (14.3)		
Diabetic kidney disease, n (%)	0 (0)		
Impaired hypoglycemia awareness, n (%)	6 (28.6)		
History of ketoacidosis, n (%)	1 (4.8)		
Anxiety or depression disorder, n (%)	2 (9.1)		

BMI-body mass index, GWG-gestational weight gain, HCLs-hybrid closed-loop system, HbA_{1c} –glycated haemoglobin.
[a] Adequacy of GWG is based on IOM (12).

second and third trimester, respectively) (Table 2). During the night, this percentage further increased, reaching 80.0 ± 11.0 % in the third semester. A total of 11 (52.4 %) and 17 (81.0 %) participants spent >70 % of their time within the pregnancy-specific target glucose range in the second and third trimester, respectively. The average glucose concentration in the third trimester was 117 mg/dl (6.5 mmol/l). However, none achieved an average glucose concentration below 115.2 mg/dl (6.4 mmol/l) in the first trimester, and only 38 % of women achieved this goal by the end of pregnancy.[1]

The results of the independent *t*-test showed that women with HbA_{1c} ≤ 6.5 % (48 mmol/mol) before pregnancy ($n = 9$) had lower TIR in the second trimesters (78.5 ± 7.6 vs. 65.9 ± 11.8, $p = 0.012$) and third trimester (80.9.3 ± 5.8 vs. 71.7 ± 7.5), but not in the first (67.3 ± 7.8 vs. 61.6 ± 9.6, $p = 0.254$).

Time spent below the pregnancy-specific glucose range was consistently low throughout the trimesters, averaging <3 %, as recommended, with no reported cases of severe hypoglycemia. One ketoacidosis event was reported in a woman who had experienced several ketoacidosis events in the past. No participant discontinued treatment with the HCLs during pregnancy or switched insulin delivery to the manual mode.

Insulin dose increased progressively throughout pregnancy (Table 2), from 0.58 ± 0.19 IU/kg/24 h in the first trimester to 0.93 ± 0.32 IU/kg/24 h in the third trimester. The carbohydrate-to-insulin ratio gradually declined from 8.6 ± 2.3 g/IU for breakfast in the first trimester, to 3.7 ± 1.9 g/IU in the third trimester, averaging a 2.3- fold decrease. A similar decline in carbohydrate-to-insulin ratio was observed for lunch and dinner. The percentage of basal insulin slightly decreased throughout pregnancy, along with a reduced need for algorithm autocorrections.

Table 2
Glycemic parameters achieved through the trimesters.

	1st trimester ($n = 14$)	2nd trimester ($n = 21$)	3rd trimester (n = 21)
HbA_{1c}			
%	6.1 ± 0.7	5.8 ± 0.5	5.9 ± 0.5
mmol/mol	43.1 ± 7.5	39.6 ± 5.8	41.3 ± 5.8
Mean sensor glucose, mg/dl | mmol/l	130.5 ± 10.4 | 7.2 ± 0.6	120.9 ± 13.4 | 6.7 ± 0.7	117.3 ± 9.1 | 6.5 ± 0.5
Day	131.0 ± 11.8 | 7.3 ± 0.7	122.1 ± 14.0 | 6.8 ± 0.8	119.1 ± 9.0 | 6.6 ± 0.5
Night	127.5 ± 11.8 | 7.1 ± 0.7	118.7 ± 13.9 | 6.6 ± 0.8	113.5 ± 12.0 | 6.3 ± 0.7
SD sensor glucose, mg/dl | mmol/l	42.7 ± 5.5 | 2.4 ± 0.3	40.0 ± 6.8 | 2.1 ± 0.4	34.7 ± 4.8 | 1.9 ± 0.3
GMI, mmol/mol	46.8 ± 2.7	44.3 ± 3.5	43.3 ± 2.4
CV, %	31.6 [30.1–34.0]	29.7 [28.3–31.9]	28.2 [27.1–32.5]
TIR, %	64.0 ± 9.0	71.3 ± 11.8	75.7 ± 8.1
Day	61.6 ± 9.2	68.9 ± 11.6	73.5 ± 7.9
Night	68.6 ± 11.5	76.0 ± 14.0	80.0 ± 11.0
TAR, %	33.4 ± 9.7	25.4 ± 12.5	21.6 ± 8.8
Day	35.5 ± 10.2	27.5 ± 12.7	23.9 ± 8.7
Night	29.3 ± 11.8	21.3 ± 14.0	11.5 [9.9–22.9]
TBR, %	2.6 ± 1.6	2.8 [2.0–3.7]	2.7 ± 1.8
Day	2.9 ± 1.7	3.4 [2.2–4.1]	2.6 ± 1.6
Night	2.1 ± 2.0	1.7 [0.8–3.1]	2.4 [1.1–3.2]
Mean sensor glucose ≤115 mg/dl (6.4 mmol/l), n (%)	0 (0)	7 (33.3)	8 (38.1)
Mean sensor glucose ≤120 mg/dl (6.7 mmol/l), n (%)	2 (14.3)	11 (52.4)	15 (71.4)
TIR > 70 %, n (%)	5 (35.7)	11 (52.4)	17 (81.0)
TBR > 4 %, n (%)	3 (21.4)	5 (23.8)	4 (19.0)
TBR > 10 %, n (%)	0 (0)	1 (4.8)	0 (0)
TAR <25 %, n (%)	2 (14.3)	10 (47.6)	15 (71.4)
Total insulin, IU	37.2 [27.1–45.5]	44.8 [41.4–56.2]	64.0 [54.9–83.9]
Total insulin per body weight, IU/kg	0.58 ± 0.19	0.63 [0.53–0.72]	0.93 ± 0.32
Daily basal insulin, %	35.7 ± 7.8	29.0 [25.0–37.0]	28.6 ± 8.9
Autocorrections, % of total daily bolus insulin delivered	9.8 ± 6.4	10 ± 8.1	8.1 ± 8.1
Autocorrections, % of total daily insulin dose delivered	5.9 ± 3.5	6.5 ± 4.8	5.3 ± 4.9
Mean daily carbs, g	217.9 ± 98.2	203.2 ± 65.0	213.5 ± 79.5
CIR-factor – breakfast	8.6 ± 2.3	6.0 ± 2.1	3.7 ± 1.9
CIR-factor – lunch	9.9 ± 2.3	6.7 ± 2.5	4.3 ± 2.1
CIR-factor – dinner	10.7 ± 2.7	7.2 ± 2.7	4.5 ± 2.0

SD-standard deviation, GMI-glucose management indicator, CV-coefficient of variation, TIR-time in range, TAR-time above range (glucose concentration > 63–140 mg/dl (7.8 mmol/mol)), TBR-time below range (glucose concentration < 63 mg/dl (3.5 mmol/l)), CIR-carbohydrate-to-insulin-ratio.
Data is presented as mean ± SD for normally distributed variables or median with interquartile ranks for non-normally distributed variables.

3.2. Maternal and neonatal outcomes

A substantial proportion of participants (57.1 %) underwent cesarean section, as indicated in Table 3. Neonatal jaundice was observed in 47.6 %[10] babies. None of the newborns were classified as SGA, yet nearly half of them were born LGA. Glycemic parameters with the strongest association with the delivery of the LGA babies were pre-conceptional average HbA_{1c} and parameters from the second trimester - average glucose concentration, pTAR, pTBR and pTIR, along with the standard deviation of sensor glucose (Fig. 1). Conversely, glycemic parameters from the first trimester did not demonstrate a significant association with the occurrence of LGA births. In the third trimester, only higher pTAR, lower pTBR and higher mean sensor glucose were associated with the delivery of the LGA babies (Fig. 1).

The receiver operating curve (ROC) analysis (Supplementary Fig. 1) illustrates that mean glucose concentration in the second trimester distinguishes women who deliver LGA baby better than mean glucose in the first or the third trimester.

Glycemic trajectories of individuals who delivered LGA infants are shown in Fig. 2. Although the majority of women reached target pTIR at the third trimester, this did not necessarily prevent the delivery of LGA babies. On the contrary, achieving a pre-pregnancy target HbA_{1c} level < 6.5 % (48 mmol/mol) almost completely prevented the delivery of LGA babies, even though glycemic control was not optimal during pregnancy. About half of women without optimal pre-pregnancy glycemic control, who attained pTIR >70 % until the second trimester, delivered appropriately for gestational age babies. Of note, 25 % of women with pre-pregnancy HbA_{1c} above the target delivered appropriately for gestational age babies, as well as 9.5 % (2/21) of women who did not reach the target pTIR in any trimester.

Table 3
Perinatal outcomes.

	Mean ± SD or n (%)
Birthweight, g	3809 ± 589
Gestational age, days	37.8 ± 1.3
Gestational age < 37 weeks	2 (9.5)
LGA	10 (47.6)
SGA	0 (0)
Cesarean section	12 (57.1)
Elective	8 (38.1)
Urgent	4 (19.0)
Preeclampsia	2 (9.1)
Eclampsia	0 (0)
Neonatal jaundice	10 (47.6)
Neonatal hypoglycemia	1 (4.8)
Birth trauma	0 (0)
Neonatal death	0 (0)
Stillbirth	0 (0)

LGA-large for gestational age, SGA-small for gestational age.

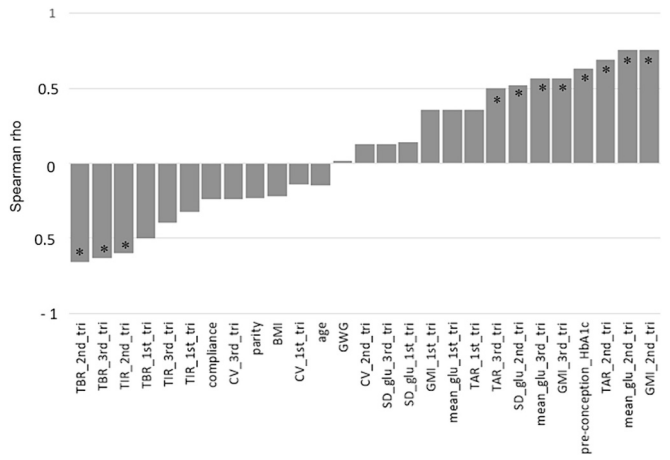

Fig. 1. Associations of different glycemic parameters with the delivery of the LGA baby.
(LEGEND: TIR-time spent within pregnancy specific range 3.5–7.8 mmol/l (63–140 mg/dl), TBR-time spent below 3.5 mmol/l (63 mg/dl), TAR-time spent above 7.8 mmol/l (140 mg/dl), 1st_tri-first trimester, 2nd_tri-second trimester, 3rd_tri-third trimester, GWG-gestational weight gain, SD-standard deviation, CV-coefficient of variation, GMI-glucose management indicator.
*Indicates statistically significant associations ($p < 0.05$)).

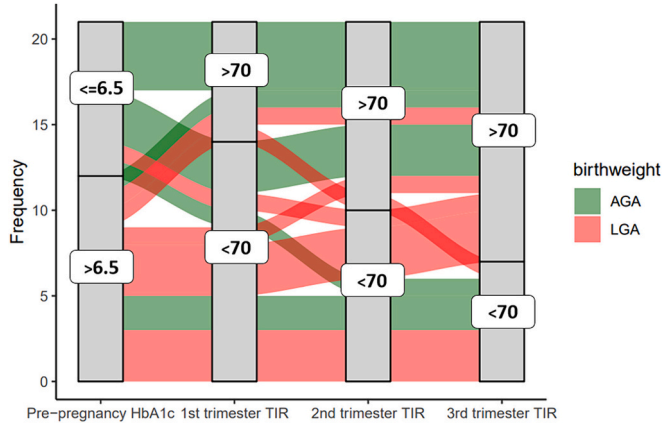

Fig. 2. Alluvial plot presenting the association of pre-pregnancy HbA_{1c} and achievement of target time in pregnancy-specific range with the birth of large-for-gestational-age babies. (In the alluvial plot every individual woman is represented by a line. Women giving birth to LGA (red) or AGA (green) infant were followed based on the achievement of glycemic targets from the pre-pregnancy period (pre-pregnancy $HbA_{1c} \leq 6{,}5$ %) throughout pregnancy (pTIR ≥70 %). LEGEND: HbA_{1c}- glycated haemoglobin; TIR – time spent within pregnancy specific range (63–140 mg/dl; 3.5–7.8 mmol/l); LGA – large-for gestational-age; AGA – appropriate-for-gestational-age).

4. Discussion

Limited data exists on the use of closed loop insulin delivery systems during type 1 diabetes pregnancy. In this study, we describe glycemic and perinatal outcomes in a cohort of women using the commercially available HCLs Minimed 780G, tracked throughout pregnancy as part of our standard clinical care. We found that, regardless of pre-pregnancy glycemic control, most women can achieve recommended glycemic goals with the use of the Minimed 780G HCLs in a real-world setting, with a low risk of hypoglycemia, even though this system has not yet been approved for use in pregnancy. Furthermore, our study demonstrates that despite good glycemic control, the delivery of a LGA baby is common. Nevertheless, efforts to attain pregnancy glycemic goals, at least until the second trimester, are crucial for prevention of the delivery of the LGA baby.

The first and currently the only closed-loop insulin delivery system approved for use in pregnancy in some countries is CamAPS, and recently, data from the randomized controlled trial were published.[6] By using the closed loop with this algorithm, a consistent 10.5 % higher time in the pregnancy-specific range was achieved compared to standard care, independent of maternal age, HbA_{1c}, pretrial insulin delivery method, or clinical site. Although this system allowed for setting lower glycemic targets in later pregnancy, i.e. 81–90 mg/dl (4.5–5.0 mmol/l) compared to the algorithm used in our study, where the lowest glucose target was set at 100 mg/dl (5.5 mmol/l) throughout the pregnancy, the mean glucose concentration attained in our study was comparable or even lower. However, observational design of our study prevents us from drawing direct comparisons with this large randomized controlled trial.[6] Similarly, higher pTIR and lower average glucose concentration during 4 weeks of only overnight use of a DANA Diabecare R Insulin Pump and the FreeStyle Navigator II closed loop system was reported.[16] However, during day-and-night usage of the same system, the proportion of pTIR, as well as mean sensor glucose concentration, were comparable.[17]

In line with this, the recently published randomized controlled trial with the Minimed 780G HCLs[8] showed that there was no difference in pTIR between Minimed 780G and the control group, however, they both started out with excellent control at baseline (HbA1c 6.5 %). The overnight pTIR was better with Minimed 780G with minimum pTBR and less GWG. Of note, our data demonstrate that similar glycemic control can be achieved with this system also outside the controlled study environment. Interestingly, three observational small cohort studies suggested that desirable glycemic control could not be reached by using the Minimed 780G system.[18–20] In these studies, women had higher average HbA_{1c} at the beginning of pregnancy compared to our cohort. The most prominent difference, however, was the lower daily insulin dose per body weight across gestation, i.e. 0.7 IU/kg vs. 0.9 IU/kg in our study in the third trimester, and a relatively small lowering of the insulin-to-carbohydrate ratio in their reports.[18–20] Since the Minimed 780G system is very efficient in preventing post-meal hypoglycemia due to safe-meal bolus module,[21,22] we could increase prandial insulin delivery to prevent postprandial hyperglycemia due to increased insulin resistance in advanced pregnancy only by timely optimization of the carbohydrate-to-insulin ratio and, if insufficient, by applying (even 50 %) higher carbohydrate amount as actually consumed (assisted carbohydrate estimation). In our study, the carbohydrate-to-insulin ratio in the third trimester was 2.3-times lower compared to the first trimester, whereas e.g. in the study from Albert L et al., it was only 1.2-times lower.[20] Additionally, throughout pregnancy, we encouraged women to pay meticulous attention to timely bolus application, diet, and regular physical activity[23]. Case reports on favorable glycemic control are available also from some other closed-loop systems, e.g. Control-IQ technology[24] or DexCom G6 sensors with an online open-source platform Nightscout.[25,26]

Importantly, despite achieving good glycemic control, 48 % of the babies delivered in our study were LGA. In the randomized controlled trial with the HCLs using Cambridge model predictive control algorithm, only 39 % of babies were LGA, although glycemic control was quite comparable in both studies.[6] On the other hand, in our study, we had numerically fewer preterm births (9.5 % vs. 45 %), urgent cesarean sections (19 % vs. 37 %), and neonatal hyperbilirubinemia (48 % vs. 68 %). The exact reason is unknown; however, one of the recent hypotheses is that better pre-pregnancy glycemic control results in less microangiopathy and consequently larger placental size and better placental function so that even mild increases in blood glucose facilitate growth acceleration.[27] Indeed, our cohort had a lower mean pre-pregnancy and early pregnancy HbA_{1c} compared to the study by Lee et al.,[6] 6.1 ± 0.7 % vs. 7.6 ± 1.1 %, respectively. Similarly, Benhalima and colleagues[8] reported a good baseline glycemic control in their study (HbA1c 6.5 ± 0.6 %), yet they observed a relatively high percentage of LGA infants (55.8

% in the HCL group and 67.4 % in the control group).

Factors most strongly associated with the delivery of the LGA baby in our study were pTIR, mean sensor glucose, and pTAR in the second trimester. Of note, a higher pTBR was a strong protective factor against delivery of the LGA baby, in line with previous reports, suggesting that the delivery of the LGA babies was prevented only in women spending substantially more time (10 %) with sensor glucose below target range as recommended by current guidelines.[2,28] Indeed, studies in healthy pregnancies have also shown that pTBR is inversely associated with the risk of LGA.[29] In this view, systems designed to avoid hypoglycemia, such as the Minimed 780G HCLs, may not be the best solution to avoid LGA births. One of the most prominent factors associated with lower risk of delivery of the LGA baby in our study was low pre-pregnancy HbA_{1c}, possibly mirroring the better capacity of those women for efficient self-management of glucose control.

Major drawback of our study is its relatively small sample size, although it is, to the best of our knowledge, the largest cohort reporting the use of the Minimed 780G system use in pregnancy outside the randomized controlled trial in a real-world setting so far. Additionally, this was not a randomized controlled trial, so we cannot know if women included would perform similarly or even better using other insulin pump systems. Nevertheless, in our previous report,[7] we have shown that the same women achieved better glycemic control using Minimed 780G HCLs compared to sensor-augmented pump. Moreover, in the present study, we did not perform an analysis of women's satisfaction with the HCLs. However, in our previous study, we presented experiences of women claiming easier attainment of glycemic goals, less stress, and more freedom in everyday food choices by using Minimed 780G HCLs compared to the use of sensor augmented pump.[7] Another important limitation of this study is the differing time of transition to the Minimed 780 HCLs. Specifically, 9 women transitioned during the first trimester, so they were not able to benefit from the system until the second trimester. Moreover, these women may be less knowledgeable and experienced about the use of the system and therefore have less gains from the system. However, we did not find any difference in the attainment of glycemic goals in this late transition to the HCLs group compared to the more experienced users. Additionally, this was not a multi-centric study, and our results could not be generalized to women treated with multiple daily injections (MDI) who transition to the HCLs during pregnancy since we did not initiate HCLs treatment in women on MDI. Lastly, due to the small sample size we could not fully account for other factors, besides pregnancy glycemic control, on adverse perinatal outcomes, especially excessive GWG on the LGA births.

In conclusion, our data show that the recommended glycemic targets for pregnancy can be achieved with the HCLs Minimed 780G in a majority of women. Furthermore, these achievements were realized in a real-world setting, outside a clinical trial. However, intensive postprandial hyperglycemia lowering with an emphasis on proper diet and regular physical activity, as well as timely insulin-to-carbohydrate ratio lowering with assisted carbohydrate estimation should not be omitted.

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CRediT authorship contribution statement

Ana Munda: Writing – review & editing, Methodology, Formal analysis, Data curation. **Chiara Kovacic:** Writing – review & editing, Data curation. **Drazenka Pongrac Barlovic:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in our paper.

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