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Real-world evidence of off-label use of commercially automated insulin delivery systems compared to multiple daily insulin injections in pregnancies complicated by type 1 diabetes

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Short running title: Real-world evidence of AID use in pregnant women with type 1 diabetes.

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ABSTRACT

Aims: To compare glycemic control and maternal–fetal outcomes of women with type 1 diabetes (T1D) using hybrid closed loop (HCL) vs. multiple daily insulin injections (MDI) plus continuous glucose monitoring (CGM).

Methods: Multicenter prospective cohort study of pregnant women with T1D in Spain. We evaluated HbA1c and time spent within (TIR), below (TBR) and above (TAR) the pregnancy-specific glucose range 3.5–7.8 mmol/L. Adjusted models were performed for adverse pregnancy outcomes including baseline maternal characteristics and center.

Results: 112 women were included (HCL n=59). Women in the HCL group had a longer duration of diabetes and higher rates of prepregnancy care. There were no between-group differences in HbA1c in any trimester. However, in the second trimester, MDI users had a greater decrease in HbA1c (-6.12±9.06 vs. -2.16 ±7.42 mmol/mol, p=0.031). No differences in TIR (3.5-7.8 mmol/L) and TAR were observed between HCL and MDI users, but with a higher total insulin dose in the second trimester (+0.13 IU/Kg/d). HCL therapy was associated with increased maternal weight gain during pregnancy ($\beta_{adjusted}$ 3.20 kg, 95%CI 0.90-5.50). Regarding neonatal outcomes, newborns of HCL users were more likely to have higher birthweight ($\beta_{adjusted}$ 279.0 g, 95% CI 39.5-518.5) and macrosomia ($OR_{adjusted}$ 3.18, 95% CI 1.05-9.67) compared to MDI users. These associations disappeared when maternal weight gain or third trimester HbA1c were included in the models.

Conclusions: In a real-world setting, HCL users gained more weight during pregnancy and had larger newborns than MDI users, while achieving similar glycemic control in terms of HbA1c and TIR.

INTRODUCTION

Despite improvement in metabolic control in recent years, pregnancies complicated by type 1 diabetes continue to have a greater risk of adverse perinatal and obstetric outcomes compared to the general population[1]. In this context, improvement in the technologies applied to diabetes could have a significant impact in a critical period such as pregnancy, where maintenance of tight glycemic control is strongly recommended[2].

The continuous glucose monitoring in pregnant women with type 1 diabetes trial (CONCEPTT) showed that the addition of continuous glucose monitoring (CGM) during pregnancy improves both glucose control and adverse neonatal outcomes (lower incidence of large for gestational age [LGA], neonatal hypoglycaemia and neonatal intensive care admissions)[3]. While the beneficial effect of CGM was comparable for women using insulin pumps or multiple daily injections (MDI), a prespecified analysis of CONCEPTT showed that MDI users were more likely to have better glycemic control throughout pregnancy and less likely to have gestational hypertension, neonatal hypoglycemia, and NICU admissions than pump users [4] . However, the pump group using CGM did not use the more advanced intensive insulin options such as hybrid closed-loop (HCL) systems which are available now.

In recent years, HCL systems have significantly improved in glycemic control and quality of life in non-pregnant people with type 1 diabetes. Currently, its usage is strongly recommended in this population[5–7]. In this line, recent data from the AiDAPT trial, a randomized clinical trial (RCT) comparing HCL using the CamAPS FX algorithm with standard care, showed a 10.5% increase in time in range (TIR) across gestation in women using the advanced insulin delivery system[8] . However, it is important to note that despite recent approval by the European Medicines Agency (EMA), the system is not yet widely available, and it is not approved by the Food and Drugs Administration (FDA) for use in the USA. Additionally, the CamAPS FX is currently only compatible with Android phones[9]. Consequently, pregnant women often rely on other commercially available systems that are not specifically designed for use during pregnancy. Although data from a limited number of case reports show promising improvements in glucose control, the lack of a control group hinders a comprehensive understanding of their full impact during pregnancy [10–12].

Despite the limited evidence, these systems have been implemented in clinical practice for the treatment of pregnancies complicated with type 1 diabetes, prompting expert guidance on their use[13] . Thus, this study aimed to assess maternal glycemic control and pregnancy outcomes in pregnant women with type 1 diabetes using HCL, compared to women with MDI plus CGM in a real clinical setting.

RESEARCH DESIGN AND METHODS

Study population

We performed an observational prospective multicenter cohort study in women with type 1 diabetes attended at 19 tertiary university hospitals in Spain between June 2020 and June 2023. The inclusion criteria were: 1) age > 18 years; 2) type 1 diabetes; and 3) singleton pregnancy. Women with pregnancy loss before 20 weeks of gestation or treatment with continuous subcutaneous insulin infusion (CSII) with CGM different from HCL were excluded. There were no additional exclusion criteria. For each HCL user selected, a consecutive pregnant woman using MDI plus CGM during pregnancy was also included. The study was approved by the ethics committee at each participating center. All the participants were informed of the protocol and signed a consent form.

Management of diabetes in pregnancy

All women received routine clinical care according to current national guidelines[14], with antenatal visits every 2 to 4 weeks and the following glycemic targets: HbA1c <48 mmol/mol (6.5%), fasting glucose 3.9–5.3 mmol/L, and post-prandial glucose values 6.1–7.8 mmol/L; 1 h postprandial and 5.6–6.7 mmol/L; 2 h postprandial. In addition, in accordance to The International Consensus on Time in Range[15], pregnancy-specific time spent within (TIR), below (TBR) and above (TAR) time between 3.5–7.8 mmol/L was recommended for pregnant women with type 1 diabetes. HbA1c was measured every 4 to 8 weeks during pregnancy and a value was registered for each trimester (first trimester: 10-14 weeks' gestation; second trimester: 24-28 weeks' gestation; and third trimester: 32-36 weeks' gestation). HbA1c analysis was performed in each local laboratory according to standard procedures, standardized against the National Glycohemoglobin Standardization Programme.

CGM system

In Spain, the use of intermittent scanned CGM is reimbursed for all individuals with type 1 diabetes since 2019, and since 2021, real-time CGM is also reimbursed for people with type 1 diabetes who are at high risk of severe hypoglycemia (those with a history of severe hypoglycemia and/or hypoglycemia unawareness)[16]. Current CGM systems have optional alarms that warn the user in case of hypoglycemia or hyperglycemia. In addition, real time CGM systems have an alarm that warns the user if the glucose is tending towards hypoglycemia or hyperglycemia. National guidelines recommend setting the hypoglycemia alarm at between 3.6- 3.9 mmol/L in the first trimester of gestation and 3.3 - 3.6 mmol/L in the second and third trimesters, and the hyperglycemia alarm between 8.9 - 10 mmol/L throughout pregnancy[17] . The CGM-related data was obtained from each specific device software (Ambulatory Glucose Profile report of 14 consecutive days).

Hybrid-closed loop

The indications for the use of HCL in Spain were the same as those for CSII therapy, mainly suboptimal glycemic control (defined as HbA1c>53 mmol/mol [7.0%]) on MDI, high-risk of severe hypoglycemia or pregnancy/pregnancy planning [17]. The HCL systems approved for use outside of pregnancy were Medtronic 780G, Tandem Control IQ, and Diabeloop. Since none of these systems have been approved for use during pregnancy, healthcare professionals discussed with all pregnant women with type 1 diabetes the potential risks and benefits, engaging in shared decision-making throughout the pregnancy. The CamAPS FX system has recently been licensed for use during pregnancy in Europe[9] . However, this system was not widely available during the study period. The configuration of the HCL systems was recorded throughout pregnancy, including the glucose target (the lowest target glucose available was 100 mg/dL [5.6 mmol/L] for Medtronic 780G and Diabeloop, and 6.3 mmol/L for Tandem Control IQ) and insulin duration (customizable only with Medtronic 780G). Time in automatic mode and carbohydrate intake were recorded too. The initial settings and the adjustments during pregnancy were decided by the physician according to routine clinical practice, aiming to achieve glycemic goals recommended by national guidelines[14]. These guidelines do not offer specific recommendations based on the HCL

system used. Additionally, no specific advice was provided in the context of the present study.

Maternal and neonatal data

We assessed baseline demographic characteristics (age at time of booking, parity, prepregnancy weight and body mass index [BMI]), diabetes-related characteristics (diabetes duration at booking, presence of micro/macrovascular complications), smoking habit, attendance to prepregnancy care program and folic acid supplementation at first antenatal visit. Pregestational BMI was calculated based on self-reported maternal weight before pregnancy in the first antenatal visit and classified into four groups: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 kg/m^2 ≤ BMI< 25 kg/m^2), overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Gestational weight gain (GWG) at the end of pregnancy was calculated as: final weight measured at the last antenatal visit – pregestational weight. According to the 2009 National Academy of Medicine (NAM) guidelines, the rate of GWG was classified into insufficient, adequate and excessive if it was below, within, or above the recommendations as follows: 12.5 – 18 kg (underweight), 11.5 – 16 kg (normal weight), 7 – 11.5 kg (overweight), and 5 - 9 kg (obese)[18].

Obstetric and neonatal data were registered: severe maternal hypoglycemia (events requiring third party assistance) during pregnancy, preeclampsia (new onset hypertension plus proteinuria above 300 mg/day)[19], caesarean section, preterm and early preterm delivery (delivery before 37 and before 34 weeks, respectively), large and small for gestational age infant (birth weight > 90th centile and < 10th centile, respectively, according to Spanish fetal growth charts that take into account sex and gestational age[20]), macrosomia (birth weight above 4000 g), neonatal hypoglycemia (glycemia 2.2 mmol/L requiring treatment in the first 24 h after delivery[21]), respiratory distress (any distress requiring treatment), admission to the neonatal intensive care unit, congenital anomalies classified according to EUROCAT [22]and perinatal mortality (fetal and infant death from 20 weeks of gestation to 4 weeks after birth[23]). Gestational age at delivery was defined as the number of completed weeks based on the last menstrual period or on the earliest ultrasound assessment if discordant.

Statistical analysis

Continuous data were compared using Student's tests and the Mann-Whitney test, according to data distribution, and categorical data using the chi-square test. The American Diabetes Association (ADA) was used as reference for HbA1c goal achievement. ADA recommends an HbA1c <48 mmol/mol (6.5%) as first trimester target and <42 mmol/mol (6.0%) in the second and third trimesters[2]. Time trend analyses for HbA1c were performed using multivariate linear regression, including the insulin delivery system and baseline levels as covariates. Due to the observational design of this study, in those adverse maternal outcomes that showed a significant association with the insulin system used in the unadjusted model, a regression model was performed. Model 1 included maternal baseline characteristics: maternal age, pregestational BMI, smoking habit, center, diabetes-related complications and diabetes duration. As a post-hoc analysis, we performed 3 models including intermediate variables: Model 2 included model 1 plus maternal GWG as continuous variable, Model 3 included model 1 plus GWG as categorical variable based on NAM guidelines, and Model 4 included model 1 plus HbA1c in the third trimester.

Since 24% of women using HCL started the system after the first antenatal visit, a sensitivity analysis was conducted by excluding this group to assess the rates of adverse pregnancy outcomes according to the insulin delivery system used. In addition, a subgroup analysis limited to women with HbA1c at least 6.5% (48 mmol/mol) at first antenatal visit was performed. In order to follow the rule of ten events per variable to avoid overfitting, adjusted models for pregnancy outcomes only included maternal age and pregestational BMI. All analyses were performed using STATA version 14.0 (Stata Corp., College Station, TX, USA). A two-sided P-value < 0.05 was considered statistically significant.

RESULTS

Participant characteristics

A total of 124 pregnant women were initially included in the study, of whom 8 were excluded due to missing obstetrical data and 4 due to discontinuation of HCL therapy during pregnancy (mean gestational age of 14.6±8.9 weeks). The reasons for discontinuation were personal reasons (2/2) and off-label use (2/2). Thus, 112 women were included in the final

analysis. Among HCL users included in the study (n=59), 14 (23.7%) started HCL therapy during gestation at a median gestational age of 16.9 (13.7-26.1) weeks. The HCL systems used were: 48 (81.4%) Medtronic 780G, 6 (10.2%) Diabeloop and 5 (8.4%) Tandem Control IQ. Among MDI users, all subjects were using CGM before pregnancy: 50 (94.3%) Freestyle libre 2, 1 (1.9%) Dexcom G6, 1 (1.9%) Freestyle libre 3 and 1 (1.9%) Dexcom One.

The mean age of the participants was 34.8±5.0 years. In comparison to MDI users, the HCL group had a longer duration of diabetes, higher rates of attendance at the prepregnancy care program and higher rates of folic acid use, without differences in pregestational HbA1c, diabetes-related complications or BMI (Table 1).

Glycemic control

At the first antenatal visit, the groups had similar median HbA1c (HCL: 47.0 [43.2-51.9] mmol/mol, 6.5 [6.1-6.9] %; MDI: 47.5 [44.3-58.5] mmol/mol, 6.5 [6.2-7.5] %; p=0.239). There was a decrease in HbA1c levels from the pregestational period to the second trimester with a slight increase from the second to the third trimester. Although, there were no between-group significant differences in HbA1c levels in any trimester (Table 2), there was a larger decrease in HbA1c from the first to the second trimester in the MDI plus CGM group compared to HCL group (mean difference of -6.12±9.06 mmol/mol [-0.56 ±0.83%] vs -2.16±7.42 mmol/mol [-0.20 ±0.68%], adjusted p= 0.031). Mean change in HbA1c from the first to the third trimester of gestation differed between groups (MDI plus CGM: Δ HbA1c -2.32±7.43mmol/mol [-0.21±0.68%], HCL: Δ HbA1c +0.82±6.02 mmol/mol [+0.07±0.56%], unadjusted p=0.040), but was no longer significant after adjustment for baseline levels (p=0.075). There were no trimester-specific differences in the proportion of women fulfilling HbA1c targets between groups (Table 2). Two women in the MDI group experienced severe hypoglycaemia during pregnancy, whereas no such events were reported among HCL users. Additionally, there were no episodes of ketoacidosis reported.

Both groups had increased time spent in the target range (3.5–7.8 mmol/L) and decreased time spent in the hyperglycemic range (> 7.8 mmol/L) throughout pregnancy, with no significant between-group differences (Table 2). In contrast, HCL users spent less time in

hypoglycemia (< 3.5 mmol/L) in the second and the third trimester compared to women with MDI group. Roughly 20% more women in the HCL achieved the target of TBR (<4%) during all three trimesters of gestation (Table 2). The whole cohort had low glycemic variability, however the HCL group had lower CV in the second and third trimesters compared to the MDI plus CGM group (Table 2). Regarding insulin dosage, higher total insulin doses were observed in the HCL group during pregnancy (second trimester: 0.63±0.23 vs. 0.76±0.23 UI/kg/day, p<0.05), primarily driven by increased preprandial insulin (Table 2).

Regarding the configuration of the HCL systems, in the first trimester the median glucose target was set at 5.55 (5.55-5.55) mmol/L, with a median insulin duration of 2 (2-2) hours and 98 (97-99)% of time HCL was working in automatic mode. These settings remained consistent across the 3 trimesters of gestation. Carbohydrate intake registered in the HCL systems increased throughout pregnancy (trimester 1: $138 \pm 40 \mathrm{g/day}$, trimester 2: $156 \pm 51 \mathrm{g/day}$, trimester 3: $165 \pm 57 \mathrm{g/day}$; p=0.013).

Pregnancy outcomes

The median gestational age at delivery was 38 (36.9-38.7) weeks, with 28.6% of preterm deliveries, without between-group differences (Table 3, Supplemental table 1). As shown in Table 3, women who used HCL therapy during pregnancy gained a median of 3.3 Kg more (95% CI 1.2-5.3) than the MDI group (Table 3). Notably, this weight gain exceeded NAM recommendations in 52.1% of HCL users compared to 25% observed in women using MDI therapy (p=0.003). These findings remained significant after adjusting for baseline characteristics such as maternal age, pregestational BMI, smoking habit, center, diabetes-related complications, and diabetes duration (GWG in kg: β 3.20, 95% CI 0.92-5.50, p=0.007; excessive GWG: OR 3.36, 95% CI 1.17-9.66, p=0.024).

Regarding birthweight, the unadjusted analyses showed that newborns of HCL users had higher weight compared to those of the MDI plus CGM group, without significant differences in LGA or macrosomia rates (Table 3). When baseline maternal characteristics were included in the regression models, both higher birthweight (β 279.0, 95% CI 39.5-518.5, p=0.023) and macrosomia (OR 3.18, 95% CI 1.05-9.67, p=0.041) were associated with the use of HCL

therapy, whereas no significant association was found between LGA and the insulin delivery system (OR 1.78, 95% CI 0.73-4.38, p=0.203). These associations were blunted when maternal weight gain (as continuous variable) or HbA1c in the third trimester were included in the adjusted models. However, when GWG was included in the model as a categorical variable (based on NAM guidelines), the association between birthweight and HCL therapy remained significant (β 278.0, 95% CI 34.8-5213, p=0.026), with no association observed for LGA or macrosomia (Supplemental Table 2). There were no between-group differences in other adverse outcomes such as caesarean section or neonatal hypoglycaemia (Table 3).

Lastly, a sensitivity analysis was performed, limiting the analysis to HCL users who started the system before pregnancy, showing similar results regarding maternal weight gain during pregnancy and birthweight (Table 4, Supplemental table 3).

Subgroup analysis in women with HbA1c≥ 6.5% (48mmol/mol) at the first antenatal visit

Ninety-one women had an available HbA1c value at the first antenatal visit, with HbA1c ≥ 6.5% (48 mmol/mol) observed in 42 of them (46.2%). In this subgroup of women, the glycemic pattern throughout gestation was similar to that observed in the whole cohort: no between-group differences in HbA1c levels in each trimester of gestation, and lower TBR and CV in the HCL group (Supplemental table 4). However, despite no significant differences in HbA1c or GMI in the first trimester of gestation, 5% of women using HCL achieved a TIR >70% compared to 0% in MDI group (p=0.027), with lower both TBR (MDI: 4[2-6]%, HCL:1.3 [1-3]%, p=0.032) and TAR (MDI: 44.5[36.5-56.5]%, HCL: 37[24-50]%, p=0.032).

In this subgroup of women, the HCL therapy was also associated with a higher weight gain in both crude and adjusted models (mean difference of 5.4Kg, 95%CI 1.5-9.3; β 4.50, 95% CI 0.25-8.76). Regarding neonatal outcomes, newborns of HCL users had a higher risk of neonatal hypoglycemia even after adjustment for maternal age and pregestational BMI (MDI: 25% HCL: 59.1%; adjusted OR 1.89, 95% CI 0.11- 6.68). Birthweight was not significant different between groups (Supplemental table 5).

DISCUSSION

In a real-world setting, the off-label use of commercial HCL systems during pregnancy achieved similar glycemic control, as measured by HbA1c and TIR, throughout pregnancy compared to MDI users. However, HCL therapy during pregnancy resulted in higher weight gain in both mothers and their newborns. To the best of our knowledge, this is the first large cohort study examining the impact of advanced insulin delivery systems in the clinical practice of pregnant women with type 1 diabetes.

In our cohort, while there were no between-group differences in HbA1c levels in each trimester, a greater reduction in HbA1c from the first to second trimester was observed in the MDI group. Similarly, more pronounced reductions in HbA1c during gestation in MDI group compared to pump users was also observed in a prespecified secondary analysis of the CONCEPTT, in this case without the automation of insulin delivery[4]. In contrast, the use of a HCL with the CampAPS FX algorithm in the AiDAPT trial resulted in an 10.5% increase in TIR compared to standard care in pregnancies complicated by type 1 diabetes, regardless of the baseline insulin delivery system (CSII or MDI)[8]. Notably, this system differs from other commercialized HCL systems as it can be specifically tailored to pregnancy-specific glucose targets. The minimum target glucose level set at 4.4mmol/L with the CampAPS FX algorithm was considerably lower than the target glucose level of 5.5 mmol/L with the Medtronic 780G or Diabeloop systems (which constituted 89.8% of the HCL group in our cohort) [9,24]. On the other hand, baseline glycemic control was not comparable between our cohort and AiDAPT trial (64.4% vs. 47.8% of TIR; 46 vs. 60 mmol/mol of HbA1c, respectively). The lower levels of HbA1c in the present study was consistent with findings from previous Spanish multicenter cohort studies[23,25,26], where the expertise of the centers and the higher rates of prepregnancy care (50-70%) may contribute to this glycemic control[27,28] . A real-world evaluation of the use of Minimed 780G among 12,870 users highlighted that a higher baseline TIR was associated with a smaller change in TIR[29]. Thus, the well-controlled baseline glycemic state might have mitigated the impact of HCL therapy in a real-word setting. However, the TIR achieved at the end of pregnancy was similar in HCL with commercial systems and with the CamAPS FX algorithm (roughly 70%). More differences were observed between control arms, but baseline characteristics precluded comparisons (55.6% vs. 69.5%,

AiDAPT trial vs our cohort, respectively). We only included women with MDI regardless of HbA1c, in contrast to the AiDAPT trial where the control arm included both MDI and CSII with HbA1c of at least 6.5% during early pregnancy[8]. This difference could suggest that this group might have faced more challenging diabetes. Overall, whether baseline maternal characteristics or system characteristics can explain the observed glycemic outcomes should be clarified in the results of an ongoing RCTs with Medtronic 780G (CRISTAL study)[30] or Tandem Control-IQ (CIRCUIT study) [31].

Interestingly, newborns of women using HCL therapy were more likely to have higher birthweight compared to the MDI group. These results were in the same line that those reported in contemporary cohorts evaluating CSII in Germany and USA, including 399 and 646 pregnancies complicated by T1D, respectively [32,33]. Wang et al. described that despite a better glycemic control in the first trimester in the CSII group, higher birthweight was observed (even after adjusted for GWG). We also observed a higher TIR in women using HCL in the subgroup of women with HbA1c at least 6.5% at the first antenatal visit. Lower glucose levels in the first weeks of gestation could lead to better placentation and, consequently, a more efficient transfer of nutrients to the fetus later in pregnancy, enhancing the likelihood of LGA[34]. This theory is supported by previous studies in which poor glycemic control and maternal vascular disease were associated with intrauterine growth restriction. In the T1D population, this unfavorable intrauterine environment leads to a restriction of macrosomia, falsely normalizing fetal growth[35–37]. Another hypothesis to explain the association between HCL and birthweight could be related to maternal weight. The excessive GWG observed in the CSII users could mediate the birthweight, given the loss of association with macrosomia when GWG was included in the adjusted models[38]. However, this effect on maternal weight was not observed in RCT such as the secondary prespecified analysis of CONCEPTT comparing CSII and MDI nor in the AiDAPT comparing HCL vs standard care (MDI or CSII)[4,8]. It is important to note that in both of these trials, the gestational age at delivery was approximately 1 week earlier (or even less in CamAPs group) compared to our findings and the data from Hauffe et al.[32]. Maternal weight gain follows a non-linear trajectory, with more notable increases observed during the final weeks of gestation[39,40]. This difference in gestational age may potentially have influenced the discrepancies observed in gestational

weight gain. Additionally, the higher insulin dosage observed in HCL group in the current study could also contribute to his phenomenon. Indeed, the impact of intensive insulin therapy on body weight has been widely described not only in the non-pregnant population, but also during a prepregnancy care program, regardless of hypoglycemia events or carbohydrate intake[41,42], and in pregnant women[43].Nevertheless, it is intriguing that higher insulin doses with use of HCL were not observed in the AiDAPT trial.

Our study has to be interpreted in the context of its limitations and strengths. Among its strengths are its multicenter nature and size. To date, this is the largest cohort study evaluating the effect of off-label use of commercial HCL during a critical period such as pregnancy in a real clinical setting [10–12]. To limit selection bias in the control group, after including an HCL user, consecutive pregnant women with MDI plus CGM were included. Furthermore, these data were collected from university hospitals with expertise in both HCL systems and obstetric management of pregnant women with diabetes. In addition to well-known maternal risk factors, the adjusted regression models included the clinical center, accounting for possible variation in clinical practice between centers. Nonetheless, limitations should also be acknowledged. First, CGM-derived data were obtained from different sensors. Nørgaard et al. showed that intermittent scanned CGM (FSL version 1) measured a clinically relevant higher percentage of TBR compared with real time CGM (Envision Pro; Medtronic) during early pregnancy without differences in mean sensor glucose. Similarly, Kristensen et al. compared FSL version 1 with Dexcom G4 during gestation with similar findings in TBR[44]. In both previous studies, intermittent scanned CGM used had no alarms, making difficult to determine if this could explain the increased TBR in this group. Although there are no comparative studies with FSL version 2 (which includes alarms) and Guardian sensor 3 (the most frequent sensors used in the MDI and HCL group, respectively), the finding regarding TBR observed in our cohort should be interpreted with caution. Second, carbohydrate intake was only available from the HCL group. Between- group differences in carbohydrate intake could play a role in the insulin doses and maternal weight gain. However, previous data from a subanalysis of the CONCEPTT study, including 93 pregnant women, showed that there were no significant differences in total energy, carbohydrate intake, or snacking behaviors of pregnant women using CSII and MDI[45]. Third,

the timing of starting HCL (before or during pregnancy) could introduce bias. Therefore, a sensitivity analysis was performed including only HCL initiated before pregnancy, which yielded the same maternal and neonatal outcomes. Fourth, patient-reported outcomes measures (PROMs) and the number of visits were not recorded. In non-pregnant populations, the implementation of HCL in real clinical practice improved several aspects of quality of life, regardless of the HCL system used[46]. However, data during pregnancy are not uniform. The AiDAiPT trial demonstrated that the use of CamAPS FX algorithm was associated with a reduction in antenatal visits, but PROMS did not differ significantly compared to standard of care[8]. Conversely, in a small case series study, reduced diabetes management burden and improved sleep were described in Control-IQ users[12]. Whether these differences are attributable to the specific HCL system used or the study design itself should be further elucidated. Finally, while randomized clinical trials primarily focus on evaluating the efficacy of interventions under optimal conditions[47] , this observational study highlights limitations inherent to real-world clinical practice, such as the use of HCL in women with more challenging diabetes and/or initially well-managed glycemic control. This data could help to design alternative approaches to enhance prenatal care for pregnant women, considering the diverse challenges encountered in practical clinical settings.

In conclusion, women using HCL systems, off-label for pregnancy use, were more likely to have higher gestational weight gain and to have newborns with higher birthweight compared to MDI users, while achieving similar glycemic control in terms of HbA1c and TIR. Further research and well-designed clinical trials are needed to fully understand the potential benefits and challenges associated with HCL systems in pregnant women with type 1 diabetes.

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Author Contributions Statement:

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Table 1. Maternal baseline characteristics according to the insulin delivery system used.

	Overall (n=112)	**MDI plus CGM (n=53)**	**HCL (n=59)**	***p* value**
Age (years)	34.8±5.0	34.5±5.2	35.0±4.8	0.557
Current smoker	4/109 (3.7)	1/49 (2.0)	3/60 (5.1)	0.223
European descent	105 (93.8)	48 (90.6)	57 (96.7)	0.441
Higher education	55/90 (61.1)	19/37 (51.4)	36/53 (67.9)	0.302
Diabetes duration (years)	17.0±8.9	13.6±8.7	20.0±8.7	<0.001*
Diabetes-related complications				
Retinopathy	20 (17.8)	6 (11.3)	14 (23.7)	0.082
Nephropathy	3 (2.7)	1 (1.9)	2 (3.4)	
Neuropathy	4 (3.6)	3 (5.6)	1 (1.7)	
Cardiovascular disease	0	0	0	
Women with >=1 episodes of severe hypoglycemia in the 2 years before pregnancy	7/103 (6.8)	5/50 (10.0)	2/53 (3.8)	0.210
Primiparous	45/107 (42.1)	20/50 (40.8)	25/57 (43.8)	0.687
Prepregnancy care program	71/110 (64.6)	26/51 (51.0)	45/59 (76.3)	0.006*
Folic acid use at first antenatal visit	41 (57.8)	11 (37.9)	30 (71.4)	0.005*
Pregestational BMI				
n	99	48	51	0.700
kg/m^2	25.3 (22.2-28.0)	24.9 (21.8-28.1)	25.6 (22.5-27.3)	
Underweight (< 18.5 kg/m^2)	0	0	0	

Normal weight (18 to < 25Kg/m^2)	48 (48.5)	25 (52.1)	23 (45.1)	
Overweight (25 to < 30Kg/m^2)	37 (37.8)	17 (35.4)	20 (39.2)	
Obesity (≥ 30 kg/m^2)	14 (14.4)	6 (12.5)	8 (15.7)	
Pregestational HbA1c				
n	105	48	57	
mmol/mol	49.7 (45.3-54.1)	49.7 (45.3-60.1)	49.7 (45.3-53.0)	0.577
%	6.7 (6.3-7.1)	6.7 (6.3-7.7)	6.7 (6.3-7)	
GA at first antenatal visit (weeks)	7.7 (6.1-10.6)	7.9 (6.3-11.7)	7.4 (6.0-9.2)	0.260

Results are given as n(%), n/N (%) in case of missing data, mean ± SD for normal distributions or median (IQR) for non-normal distributions

Abbreviations: BMI, body mass index, GA, gestational age

Table 2. Glycemic outcomes in each trimester of gestation according to the insulin delivery system used.

	Trimester 1		Trimester 2		Trimester 3	
	MDI plus CGM	**HCL**	**MDI plus CGM**	**HCL**	**MDI plus CGM**	**HCL**
HbA1c						
n	49	49	48	55	42	47
mmol/mol	48.1±9.3	46.5±8.0	42.5±6.2	44.4±6.8	44.9±5.4	45.8±5.4
%	6.54±0.85	6.41±0.73	6.04±0.56	6.21±0.62	6.25±0.49	6.34±0.49
Attainment HbA1c target[a]	27 (55.1)	30 (61.2)	20 (41.7)	18 (32.7)	12 (28.6)	10 (21.3)
GMI						
n	42	42	47	48	45	50
mmol/mol	46.7±5.7	47.3±3.6	46.0±6.5	47.1±2.8	45.0±4.6	46.1±3.5
%	6.42±0.53	6.48±0.33	6.40±0.60	6.46±0.25	6.27±0.42	6.37±0.32
Mean sensor glucose						
n	45	53	50	57	49	58
mmol/L	7.16±1.17	7.28±0.78	7.16±1.06	7.28±0.72	6.83±0.94	6.94±0.72
mg/dL	128.9±21.1	131.0±14.0	128.9±19.1	131.0±13.0	123.9±16.9	124.9±13.0
TIR 3.5-7.8 mmol/L						
n	47	52	50	59	49	58
%	61.8±15.6	64.6±13.3	62.3±17.4	65.2±12.8	69.5±15.0	70.4±13.0

TIR >70%, n (%)	14 (28.8)	17 (32.7)	16 (32.0)	19 (32.2)	24 (49.0)	26 (44.8)
TBR <3.5mmol/L						
n	47	54	50	60	49	59
%	4 (2-6)	3 (1-5)	3 (1-6)	2 (1-3)*	3 (1-6)	1 (0-2)*
TBR < 4%, n (%)	22 (46.8)	37 (68.5)*	29 (58.0)	48 (81.4)*	30 (61.2)	52 (88.1)*
TAR >8.8mmol/L						
n	47	52	50	59	49	58
%	33 (22-46)	31 (22.5-40.5)	31 (24-44)	33 (24-41)	27 (13-37)	29.5 (17-37)
TAR < 25%, n (%)	15 (31.9)	18 (34.6)	14 (28.0)	16 (27.1)	21 (42.9)	22 (37.9)
CV of glucose						
n	44	47	49	54	46	54
%	34.9±6.1	32.9±5.7	31.9±5.8	29.1±4.7*	29.1±5.4	27.2±4.3*
CV < 36%, n(%)	27 (61.4)	34 (72.3)	38 (77.6)	48 (88.9)	42 (91.3)	54 (100)*
Insulin dose						
n	39	42	37	54	37	56
IU/Kg*day	0.59±0.22	0.58±0.16	0.63±0.23	0.76±0.23*	0.73±0.25	0.87±0.37
Bolus insulin						
n	46	45	45	57	42	59
% total dose	49.2±13.5	63.0±11.3*	51.8±12.5	64.7±8.6*	54.0±11.5	64.1±10.4*

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y automated insulin delivery systems compared to multiple daily insulin injections in pregnancies complicated by type 1 diabetes (DOI: 10.1089/dia.2023.0594)
d and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

IU/Day	19.3±9.4	25.1±8.9*	24.1±12.0	38.2±15.4*	30.1±15.0	45.3±19.0*
Basal insulin						
n	51	50	45	57	42	59
% total dose	50.8±13.5	37.0±11.3*	48.2±12.5	35.3±8.6*	46.0±11.2	35.9±10.4*
IU/Day	20.3±9.3	16.1±7.9*	22.1±9.6	21.7±11.1	25.9±12.3	26.70±17.9
Sensor use[b]						
n	44	50	47	52	44	52
%	99 (95.5-100)	95 (92-98)	98 (93-100)	94 (90.5-98)*	97.5 (93-100)	96 (91.5-98)
use > 70%, n (%)	43 (97.7)	49 (98.0)	44 (95.7)	51 (98.1)	42 (97.7)	52 (100)

Results are given as n(%), mean ± SD for normal distributions or median (IQR) for non-normal distributions. Trimester 1: 10-14 weeks' gestation; Trimester 2: 24-28 weeks' gestation; and Trimester 3: 32-36 weeks' gestation.

* $p<0.05$ vs MDI plus CGM

[a] Percentage of women fulling HbA1c target according ADA criteria. ADA recommends an HbA1c value 48 mmol/mol as in the first trimester and < 42 mmol/mol in the second and third trimesters.

[b] Percentage of time that data sensor is available.

Abbreviations: ADA, American Diabetes Association; CV, coefficient variation; GMI, glucose management indicator; TAR, time above range; TBR, time below range; TIR, time in range.

Table 3. Pregnancy outcomes according to the insulin delivery system used.

	Overall (n=112)	**MDI plus CGM (n=53)**	**HCL (n=59)**	***p* value[a]**
GA at delivery (weeks)	38.0 (36.9-38.7)	38.0 (36.7-38.7)	38.0 (37.0-38.6)	0.891
Gestational weight gain				
n	91	41	50	
Weigh gain (Kg)	13.1±5.2	11.3±5.0	14.6±5.0	0.008*
Inadequate	33 (37.5)	18 (45.0)	15 (31.3)	0.003*
Adequate	20 (22.7)	12 (30.0)	18 (16.7)	
Excessive	35 (39.8)	10 (25.0)	25 (52.1)	
Preterm birth				
Preterm < 37 weeks	32 (28.6)	16 (30.2)	16 (27.1)	0.720
Early preterm < 34 weeks	3 (2.7)	2 (3.8)	1 (1.7)	0.496
Cesarean section	62 (56.4)	28 (54.9)	34 (57.6)	0.774
Preeclampsia	17/107 (15.9)	7/51 (13.7)	10/56 (17.9)	0.559
Birthweight				
Birthweight				
n	111	52	58	
g	3571±557	3456±548	3675±549	0.039*
SGA	0	0	0	
LGA	70/110 (63.6)	30/52 (57.7)	40/58 (69.0)	0.220
Macrosomia (≥4000g)	27/110 (24.6)	9/52 (17.3)	18/58 (31.3)	0.095
Neonatal hypoglycemia	33/101 (32.7)	10/44 (22.7)	23/57 (40.4)	0.061
Respiratory distress	14/101 (13.9)	6/45 (13.3)	8/56 (14.3)	0.664
Neonatal intensive care unit	15/106 (14.2)	8/48 (16.7)	7/58 (12.1)	0.499
Congenital anomaly	5/99 (5)	2/45 (4.4)	3/54 (5.6)	0.330
Perinatal mortality	1	1	0	-

Results are given as n(%), n/N (%) in case of missing data, mean ± SD for normal distributions or median (IQR) for non-normal distributions

Abbreviations: GA, gestational age; LGA, large-for-gestational age infant (>90th centile); SGA, small-for-gestational age infant (<10th centile)

[a] unadjusted p value

Table 4. Pregnancy outcomes according to the system of insulin delivery used. Sensitivity analysis limited to women who started HCL therapy before pregnancy.

	Overall (n=98)	**CGM + MDI (n=53)**	**HCL (n=45)**	***p* value***
GA at delivery (weeks)	38.1 (37-38.7)	38 (36.7-38.7)	38.1 (37.1-38.6)	0.983
Weight gain				
n	82	41	41	
Weigh gain (Kg)	12.7±5.2	11.3±5.0	14.4±5.1	**0.007**
Inadequate	31 (39.2)	18 (45)	13 (33.3)	0.086
Adequate	19 (24.1)	12 (30.0)	7 (18.0)	
Excessive	29 (36.7)	10 (25)	19 (48.7)	
Preterm birth				
Preterm < 37 weeks	27 (27.6)	16 (30.2)	11 (24.4)	0.526
Early preterm < 34 weeks	2 (2.04)	2 (3.8)	0	0.188
Cesarean section	53 (55.2)	28 (54.9)	25 (55.6)	0.949
Preeclampsia	15/95 (15.8)	7/51 (13.7)	8/44 (18.2)	0.553
Birthweight				
Birthweight				
n	97	52	45	
g	3574±546	3456±548	3710±517	**0.021**
SGA	0	0	0	
LGA	63/97 (65.0)	30/52 (57.7)	33/45 (73.3)	0.107
Macrosomia (≥4000g)	23/97 (23.7)	9/52 (17.3)	14/45 (31.1)	0.111
Neonatal hypoglycemia	26/88 (29.6)	10/44 (22.7)	16/44 (36.7)	0.161
Respiratory distress	11/89 (12.4)	6/45 (13.3)	5/44 (11.4)	0.778
Neonatal intensive care unit	13/92 (14.1)	8/48 (16.7)	5/44 (11.4)	0.466
Congenital anomaly	4/86 (4.7)	2/45 (4.4)	2/41 (4.9)	0.510
Perinatal mortality	1	1	0	-

Results are given as n(%), n/N (%) in case of missing data, mean ± SD for normal distributions or median (IQR) for non-normal distributions

Abbreviations: GA, gestational age; LGA, large-for-gestational age infant (>90th centile); SGA, small-for-gestational age infant (<10th centile)

* unadjusted p value