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Prepregnancy care in women with type 1 diabetes improves HbA_{1c} and glucose variability without worsening hypoglycaemia time and awareness Glycaemic variability during prepregnancy care

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ABSTRACT

Aims: To evaluate the impact of a prepregnancy care (PPC) programme, beyond HbA_{1c}, on hypoglycaemia awareness and glycaemic variability (GV).

Methods: Prospective pilot study. We selected women with Type 1 diabetes who initiated a PPC programme with normal hypoglycaemia awareness (n = 24). Hypoglycaemia awareness, hypoglycaemic events and GV derived from masked-continuous glucose monitoring were evaluated in the first visit and within 2 weeks after pregnancy confirmation.

Results: The duration was 16.5 ± 13.0 months. HbA_{1c} significantly decreased (−0.8 ± 0.7; $p < 0.001$). The Clarke score increased (0[0–1] vs. 1[0–2] points, $p = 0.164$), 2 out of 24 were reclassified as having impaired awareness of hypoglycaemia and 2 presented severe hypoglycaemia. GV decreased: standard deviation ($p = 0.008$), coefficient of variation ($p = 0.021$), mean amplitude of glycaemic excursions ($p = 0.007$), average daily risk range ($p < 0.001$), J-index ($p = 0.010$), high blood glucose index (HBGI) ($p = 0.004$), continuous overall net glycaemic action (CONGA) ($p = 0.018$), mean of daily differences ($p = 0.045$) and glycaemic risk assessment diabetes equation ($p = 0.012$). Final HbA_{1c} was associated with baseline J-index, CONGA and HBGI ($\beta = 0.535$, $\beta = 0.466$, $\beta = 0.534$, respectively; $p < 0.05$).

Conclusions: A PPC programme improved HbA_{1c} as well as GV with no significant impact on hypoglycaemia awareness. Moreover, GV could help to identify women less likely to achieve glycaemic targets. Larger studies are needed to confirm these results.

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1. Introduction

The relationship between type 1 diabetes in pregnancy and adverse neonatal outcomes is well known [1–3]. It is therefore recommended that all women of childbearing age with type 1 diabetes plan pregnancy in order to achieve optimal glycaemic control, evaluate diabetes-related complications and refresh their knowledge and skills about diabetes [4,5]. Prepregnancy care (PPC) has been associated with an 80% reduction of serious adverse pregnancy outcomes (major congenital malformation, stillbirth or neonatal death) and lower rates of very premature delivery [6–9].

In a non-pregnant population with type 1 diabetes, the Diabetes Control and Complications Trial showed an increased risk of severe hypoglycaemia (SH) in the intensive insulin therapy group [10]. Moreover, recurrent episodes of non-SH promote impaired awareness of hypoglycaemia, increasing the risk of SH 3-fold [11,12]. In the setting of PPC, only the incidence of SH has been evaluated. PPC does not seem to increase the rate of SH, but the duration of PCC has been found to be an independent risk factor for SH [6,13].

In the last years, the role of glycaemic variability (GV) as a predictor of diabetes-related complications and pregnancy outcomes has emerged. Glycated haemoglobin (HbA_{1c}) is an indirect measure of average glycaemia; however, it is only able to predict 8% of SH episodes, with GV being an additional tool to assess the risk of SH [14]. Recent studies on pregnancy have shown that some GV measurements could explain part of the excess risk still observed in women with type 1 diabetes, despite well-controlled diabetes (in terms of HbA_{1c}) [15–17].

Overall, these data demonstrate that knowledge on the implications of PPC beyond HbA_{1c} is scarce. Although an increase in SH rates has not been observed during the PPC period, there is no data regarding repeated non-SH, hypoglycaemia awareness or GV. Thus, the aim of this prospective study was to evaluate changes in hypoglycaemia awareness and the glucose profile derived from continuous glucose monitoring (CGM) during a PPC programme.

2. Material and methods

We conducted a prospective study including women who initiated a PPC programme in the Diabetes Unit of a tertiary hospital with the following criteria: (1) >18 years old, (2) Type 1 diabetes duration >5 years, and (3) normal hypoglycaemia awareness. The Clarke test (validated Spanish version) was used to evaluate hypoglycaemia awareness [18]. Normal hypoglycaemia awareness was defined as a Clarke score ≤ 3.

The study was approved by the Ethics Committee of *Hospital Clínic de Barcelona*, and written informed consent was obtained from all participants.

2.1. Study design

At baseline, we collected demographic data and the medical history of all the participants, and a physical examination was performed (weight, blood pressure and waist/hip ratio obtained by standardized methods). The number of previous hypoglycaemic episodes (2 weeks and 2 years previously for non-SH and SH, respectively) was also registered. Capillary glycaemia <3.9 mmol/l was considered as a non-SH episode, and SH episodes were defined as those requiring assistance from a third party. Microvascular complications were screened by digital retinal photography in women with no history of retinopathy, the first urine sample collection (albumin-to-creatinine ratio) and evaluation of symptoms of neuropathy. The presence of macrovascular complications was defined as a history of ischaemic heart disease or stroke.

After enrolment, the HbA_{1c} value (National Glycohemoglobin Standardization Program [NGSP] DCCT Tosoh G8 Automated HPLC; Tosoh Bioscience Inc., South San Francisco, CA, USA; normal range 4.0–6.0% [20–42 mmol/mol]) and professional-CGM data (iPro™ 2 device; Medtronic, Northridge, CA) were obtained.

The PPC programme is described below. In cases of lengthy PPC, screening for diabetes-related complications was repeated according to guidelines [19]. Weight and blood pressure were obtained every visit until the end of the follow-up. At each visit, glycaemic control was checked in the logbook containing self-monitoring blood glucose (SMBG) values or by downloading data from either glucometers or insulin pump in specific diabetes management computer platforms, when required.

Follow-up ended when the women became pregnant. The goals of glycaemic control during pregnancy were the same as during the PPC period. Within 2 weeks after pregnancy confirmation, the participants were re-evaluated for metabolic control, number of hypoglycaemic episodes (non-SH/week and SH), hypoglycaemia awareness (using the Clarke test) and professional-CGM data.

2.2. PPC programme

Women planning to become pregnant in the near future were referred to initiate the PPC programme. During the programme, an endocrinologist and diabetes specialist nurse performed visits every 4–8 weeks. Women were advised to perform SMBG both before and one hour after meals, at bedtime, and occasionally at night. The goals were to achieve preprandial capillary glucose levels <5.3 mmol/l, 1-hour postprandial capillary glucose <7.8 mmol/l and $HbA_{1c} < 6.5\%$ (48 mmol/mol). Moreover, women were trained to reinforce self-management skills. Medical professional recommendation for pregnancy (and discontinue contraception) was given to women achieving $HbA_{1c} < 6.5\%$ (48 mmol/mol) on 2 consecutive visits or $HbA_{1c} < 7\%$ (53 mmol/mol) if they had repeated episodes of SH. From the beginning of the programme, the women were advised to start taking vitamin supplementation (folic acid: 5 mg/day and iodine: 200 mcg/day), and when the HbA_{1c} target was achieved, they were advised to discontinue contraindicated drugs such as statins, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

2.3. CGM data

Sensor data collected during the 6-day monitoring period, available at the CareLink iPro online database were: hypoglycaemic, normoglycaemiac and hyperglycaemic time (defined as percentage of time spent with glucose values <3.9 mmol/l, between 3.9–7.8 mmol/l, and >7.8 mmol/l, respectively).

Furthermore, CGM-based metrics of GV were obtained using EasyGV software v.9 [20,21] and included: standard deviation (SD), coefficient of variation (CV), M-value, mean amplitude of glycaemic excursions (MAGE), lability index (LI), average daily risk range (ADRR), j-Index, low blood glucose index (LBGI) and high blood glucose index (HBGI), continuous overall net glycaemic action (CONGA), mean of daily differences (MDD), glycaemic risk assessment diabetes equation (GRADE), and mean average glucose (MAG). Sensor data were masked until the end of the study.

2.4. Statistical analyses

Data are expressed as mean ± SD or N (percentage), except where stated otherwise. To evaluate changes throughout the study the Student's t test for paired data (normally distributed variables) or the McNemar test (categorical variables) was used. Correlations between continuous variables were performed using the Pearson correlation test.

Models of multivariate linear regression were used to test predictors of HbA_{1c} at the end of the study: (a) baseline HbA_{1c}, diabetes duration, follow-up duration and SMBG per day; (b) baseline HbA_{1c}, baseline levels of GV metrics, follow-up duration and SMBG per day.

Since the impact of PPC on hypoglycaemia awareness has not been previously reported, we considered this to be a pilot study (no sample size calculation was attempted). P values <0.05 were considered statistically significant. All statistical calculations were performed with the STATA 14.0 statistical package.

Table 1 – Baseline characteristics of the women included in the study.

	n = 24
Demographic characteristics	
Age (years)	33.8 ± 3.6
White ethnicity	25 (1 0 0)
Current smoker	5 (20.8)
Level of education	
Primary	2 (8.3)
Secondary	7 (29.2)
University	15 (62.5)
Body mass index (kg/m^2)	24.0 ± 3.6
Under weight (<18.5)	0
Normal weight (18.5–24.9)	19 (79.2)
Overweight (25–29.9)	3 (8.3)
Obese (≥30)	3 (12.5)
Waist/hip ratio	0.78 ± 0.05
Regular physical activity (>3.5 h per week)	3 (12.5)
Hypertension	1 (4.2)
Dyslipidaemia	3 (12.5)
Hypothyroidism	21 (87.5)
Primiparous	13 (54.2)
Diabetes status	
Diabetes duration (years)	16.3 ± 7.1
Presence of lipodystrophy	15 (62.5)
Insulin pump therapy	8 (33.3)
Insulin analogs*	24 (1 0 0)
Diabetic complications	
Retinopathy	5 (20.8)
Nephropathy	1 (4.2)
Neuropathy	2 (8.4)
Cardiovascular disease	0

Data are expressed as mean ± standard deviation and n (percentage). Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or as taking antihypertensive drugs. Dyslipidaemia was defined as the need for lipid-lowering drugs.

* All patients were using both long-acting and/or rapid-acting insulin analogs.

3. Results

A total of 35 participants were recruited. Ten dropped out of the PPC programme: 4 due to infertility, 3 with family problems and 3 for unexplained reasons. One patient was excluded for the final analysis because real-time CGM was initiated during PPC (sensor-augmented pump therapy). The baseline data of women who completed the study are shown in Table 1.

3.1. Metabolic control

The duration of the study was 16.5 ± 13.2 months. The final visit was at 10.6 ± 1.4 weeks of gestation. During follow-up, 66.7% of women achieved HbA_{1c} levels <6.5% (48 mmol/mol), and 87.5% presented HbA_{1c} levels <7% (53 mmol/mol). Almost the whole cohort (91.7%) obtained medical professional recommendation for pregnancy within a median time of 5.9 ± 6.6 months. Tables 2 and 3 show changes in HbA_{1c}, weight and insulin requirements throughout the study and the time spent on target. Compared to the baseline visit, SMBG per day increased (from 5.2 ± 2.3 to 6.9 ± 2.3 analyses/day at the end of the study; p = 0.001). The final HbA_{1c} was directly related to baseline HbA_{1c} values (r = 0.638, p = 0.001). This association remained statistically significant after adjustment for diabetes duration, duration of follow-up and SMBG per day (β = 0.866, p < 0.001).

During the study, 1 participant started insulin pump therapy. No episode of diabetic ketoacidosis was presented during the follow-up.

3.2. Hypoglycaemic events and hypoglycaemia awareness

At baseline, no women had presented SH within the previous 2 years. A total of 4 SH were reported during the follow-up, 3 in the PPC period (all in the same woman) and 1 in the first week of gestation (0.08 SH/patient-year). Non-SH events increased compared to baseline (8.3 ± 3.4 non-SH/week first visit vs. 10.60 ± 3.76 non-SH/week last visit; p = 0.03) without correlation with SMBG per day. Evaluating sensor data, no changes in the time in hypoglycaemia were observed between the first and last visit (Table 3).

Table 2 – Metabolic control throughout the study.

	Baseline	Last PPC visit	Final visit	p[1]	p[2]	p[3]
HbA_{1c} (mmol/mol)	53.5 ± 7.8	46.2 ± 7.6	45.0 ± 7.2	<0.001	<0.001	0.297
HbA_{1c} (%)	7.1 ± 0.7	6.4 ± 0.7	6.3 ± 0.7	<0.001	<0.001	0.297
Total insulin doses (IU/kg)	0.60 ± 0.19	0.58 ± 0.17	0.58 ± 0.18	0.452	0.501	0.927
Weight (kg)	63.9 ± 10.8	65.2 ± 12.5	67.4 ± 11.9	0.056	<0.001	<0.001

Data are expressed as mean ± standard deviation.
The last prepregnancy care (PPC) visit was considered as the visit before the last menstrual period.
p = Student's t test for paired data: (1) Baseline vs. last PPC visit; (2) Baseline vs. final visit; (3) Last PPC vs. final visit.

Table 3 – Data derived from continuous glucose monitoring.

Variable	Time of the evaluation during the study		p
	First visit	Last visit	
Time on target (%) (glycaemia 3.9–7.8 mmol/l)	48.25 ± 16.88	57.75 ± 13.24	**0.016**
Time in hyperglycaemia (%) (glycaemia > 7.8 mmol/l)	34.08 ± 14.07	26.17 ± 14.40	**0.034**
Time in hypoglycaemia (%)			
Level 1 (<3.9 mmol/l)	15.91 ± 7.72	15.95 ± 9.86	0.985
Level 2 (<3mmol/l)	5.63 ± 5.12	4.83 ± 7.07	0.648
Standard deviation (mmol/l)	2.91 ± 0.78	2.40 ± 0.74	**0.003**
Coefficient of variation (%)	42.18 ± 9.41	37.02 ± 9.37	**0.021**
M-value	12.52 ± 7.54	10.00 ± 6.91	0.192
MAGE (mmol/l)	5.93 ± 1.98	4.75 ± 1.45	**0.007**
LI	4.61 ± 1.95	3.94 ± 1.89	0.121
ADDR	20.20 ± 9.09	14.02 ± 7.15	**<0.001**
J-index	31.87 ± 10.64	26.09 ± 9.32	**0.010**
LBGI	7.76 ± 3.71	6.47 ± 3.83	0.202
HBGI	6.55 ± 3.13	4.64 ± 2.45	**0.004**
CONGA	6.04 ± 0.98	5.48 ± 0.99	**0.018**
MODD	3.10 ± 0.88	2.65 ± 1.02	**0.045**
GRADE	4.67 ± 2.41	3.36 ± 1.98	**0.012**
MAG (mmol/l)	1.95 ± 0.50	1.80 ± 0.43	0.160

Data are expressed as mean ± standard deviation. p = Student's t test for paired data. ADDR: average daily risk range; CONGA: continuous overall net glycaemic action; GRADE: glycaemic risk assessment diabetes equation HBGI: high blood glucose index; LBGI: low blood glucose index; LI: lability index; MAG: mean average glucose; MAGE: mean amplitude of glycaemic excursions; MODD: mean of daily differences; SD: standard deviation.

Regarding hypoglycaemia awareness, at baseline the women presented a median Clarke score of 0 [0–1] points. During follow-up, 37.5% of the participants increased at least one point in the Clarke test with a median score of 1 [0–2] point (p = 0.164) at the end of the study. Two out of the 24 (8.3%) participants were reclassified as having impaired awareness of hypoglycaemia (Clarke score > 3). The evolution of the Clarke score from the first to the last visit is shown in Fig. 1. Diabetes duration, follow-up duration, SMBG per day, baseline Clarke score and time in hypoglycaemia were not associated with changes in the Clarke score.

3.3. *Glycaemic variability*

In relation to changes in GV parameters, a significant reduction was found in SD (p = 0.008), CV (p = 0.021), MAGE (p = 0.007), ADDR (p < 0.001), J-index (p = 0.010), HBGI (p = 0.004), CONGA (p = 0.018), MODD (p = 0.045) and GRADE (p = 0.012) (Table 3). A reduction in these measures was not related to the final HbA_{1c}, the duration of PPC or SMBG per day. However, a higher baseline J-index, CONGA and HBGI were predictors of higher HbA_{1c} values at the end of the study (β = 0.535, p = 0.031; β = 0.466, p = 0.044; β = 0.534, p = 0.046; respectively) even after adjustment for diabetes duration, follow-up duration, baseline HbA_{1c} and SMBG per day.

4. Discussion

In this pilot study, we found that the expected improvement in glycaemic control during PPC was accompanied by a reduction in GV. This intensification in metabolic control was not associated with an increased time in hypoglycaemia or a loss of hypoglycaemia awareness. To the best of our knowledge, this is the first study to prospectively evaluate the glucose profile derived from CGM and hypoglycaemia awareness during a critical period such as PPC.

Metabolic control improved in our cohort throughout the PPC follow-up, with stabilization in the gestational period. Indeed, 87.5% of women achieved an HbA1c < 7% (53 mmol/mol), which is higher than in previously published studies

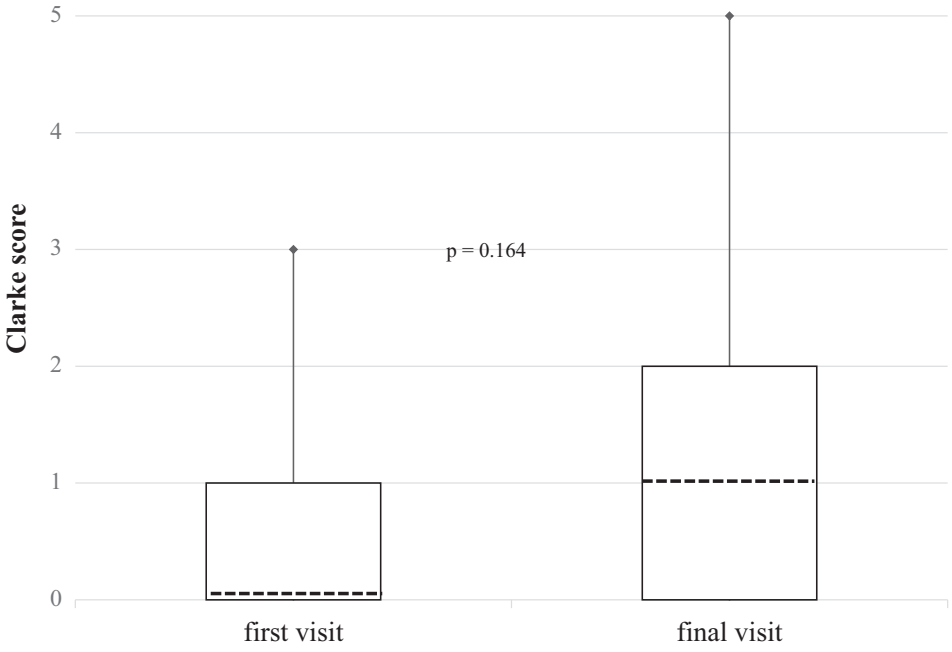

Fig. 1 – Distribution of the Clarke score in the first and the last visit of the follow-up. Clarke score is shown with box plots. The dashed line of each box represents the median, and the lower and upper boundaries of the box represent the 25th and 75th percentiles, respectively. Whiskers are drawn to the highest value that is within 1.5× (interquartil range) above the 75th percentile. p: univariate analysis: First vs. last visit.

(47.3–75%) [6,7,13]. García-Patterson *et al.* described no changes in HbA_{1c} levels (compared to prepregnancy visit) until 13 weeks of gestation [22]. These findings support our results, in which no differences in HbA_{1c} levels were observed during the gestational period (10.27 ± 1.5 weeks of gestation). Despite this intensification in metabolic control, time in hypoglycaemia did not differ between both periods (first and last visit) but 4 SH occurred and non-SH events increased. A previous study by our group, in a larger cohort, showed similar results related to hypoglycaemic events (0.119 SH/patient-year during PPC in the previous study vs 0.08 SH/patient-year in the current study) [13]. Although PPC did not significantly increase the incidence of SH, lengthy of PPC has been found as an independent risk factor for SH in this period. Moreover, educative intervention and frequent clinic visits during this time would have allowed to reduce the duration of each hypoglycaemic event without an impact on hypoglycaemia time assessed by CGM. On the other hand, a trend towards worse hypoglycaemia awareness was found, although this was not statistically significant perhaps because of the short length of the PPC period. Moreover, the use of insulin analogues and the high proportion of insulin pumps (known as protective factors) could have reduced the impact on hypoglycaemia awareness [23]. It would be interesting to investigate if the use of new technologies such as real time-CGM during PPC has the same effect on hypoglycaemia awareness as in a non-pregnant type 1 diabetes population [24].

Besides HbA_{1c}, a reduction in several GV metrics was observed. At baseline, our cohort was well controlled with normal hypoglycaemia awareness but had unstable glucose levels defined as CV ≥ 36% according to the International Consensus on Use of Continuous Glucose Monitoring [25]. Nonetheless, our PPC achieved a reduction in both HbA_{1c} and GV with no significant changes in LBGI, a specific predictive measure of SH risk. Moreover, CGM provided a potential source of data (higher baseline SD, HBGI and ADDR) to identify women with greater difficulty in achieving the HbA_{1c} target during PPC. However, previous studies evaluating GV and pregnancy did not take into account the PPC period. Higher GV during pregnancy was associated with an increased risk of infants large for gestational age but the impact of PPC, beyond HbA_{1c}, was not described [15,16,26]. In the planning pregnancy cohort of the CONCEPTT trial, at 24 weeks of PPC, GV metrics (SD, CV and MAGE) did not change in either the CGM or the control group. No information about GV was described in the women who conceived during 24 weeks of PPC [27]. Our cohort had a similar baseline GV (41% in our study vs. 40–38% in the CONCEPTT trial), but the PPC period was completely evaluated (16.5 ± 13.0 months) and a tighter HbA_{1c} was recommended (6.5% [48 mmol/mol] in our cohort vs. 7% [53 mmol/l] in the CONCEPTT trial). These characteristics could explain the differences in GV. On the other hand, our findings were in accordance with previous data showing that an educational intervention (one of the bases of PPC) played a role in improving GV regardless of the type of insulin delivery [28].

The main strength of our study was the prospective and pragmatic design that evaluated PPC in routine care. Our choice of the Clarke questionnaire as a mandatory baseline criterion was based on its sensitivity (100%) to identify people who have impaired awareness of hypoglycaemia. Its lower false negative rate avoids misclassification of unawareness [29], an independent risk factor of SH which could be a bias in PPC-related hypoglycaemic events. Additionally, although

GV measures could be obtained by both SMBG and CGM, interstitial glucose measurement at 5 min intervals provides a more comprehensive record, being CGM the gold standard method for GV. Furthermore, masked CGM-data avoided treatment modifications by the medical team and allowed real interpretation of the glucose profile throughout PPC.

Nonetheless, our study also has limitations. Firstly, the sample size was small which may explain in part the reason why no differences were found in the Clarke score, despite an 8.3% of patients were reclassified to impaired awareness of hypoglycaemia. Secondly, the study finished with pregnancy confirmation which may have interfered in the interpretation of sensor data due to the physiological changes in the glycaemic profile during pregnancy. In a previous study, significant changes in mean blood glucose and HbA_{1c} (compared to prepregnancy period) were described after 11 and 13 weeks of gestation [22]. In our study, the last visit was performed at very early pregnancy (10 weeks of gestation) limiting the possible effect of pregnancy on the glucose profile. On the other hand, almost 1 in 3 women dropped out from the follow-up. This rate is similar to that found in a previous study by our group evaluating PPC in a larger cohort (n = 104) [13]. Drop out from the PPC was related to older age and lengthy follow-up, but no differences were found regarding hypoglycaemia awareness. Finally, we did not include a control group. It would be interesting to evaluate if a specific PPC for women with impaired awareness of hypoglycaemia would achieve the same results.

In summary, in a cohort of women with type 1 diabetes with normal hypoglycaemia awareness, the intensification of glycaemic control in the setting of PPC not only improved metabolic control based on HbA_{1c} but also reduced GV without a significant impact on hypoglycaemia awareness. In addition, some of the GV parameters could help to identify women less likely to achieve the glycaemic targets. Larger studies are needed to confirm these results and evaluate the effect of the changes in GV during the PPC period on pregnancy outcomes.

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Declaration of Competing Interest

No competing financial interests exist. All authors declared that they have no duality of interest associated with this manuscript.

REFERENCES

[1] Macintosh MCM, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177. https://doi.org/10.1136/bmj.38856.692986.AE.

[2] Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. Diab Care 2009;32:2005–9. https://doi.org/10.2337/dc09-0656.

[3] Tennant PWG, Glinianaia SV, Bilous RW, Rankin J, Bell R. Pre-existing diabetes, maternal glycated haemoglobin, and the risks of fetal and infant death: a population-based study. Diabetologia 2014;57:285–94. https://doi.org/10.1007/s00125-013-3108-5.

[4] Asistencia a la gestante con diabetes. Guía de práctica clínica actualizada en 2014. Av En Diabetol 2015;31:45–59. https://doi.org/10.1016/j.avdiab.2014.12.001.

[5] Association AD. 14. Management of diabetes in pregnancy: standards of medical care in diabetes—2019. Diab Care 2019;42:S165–72. https://doi.org/10.2337/DC19-S014.

[6] Temple RC, Aldridge VJ, Murphy HR. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. Diab Care 2006;29:1744–9. https://doi.org/10.2337/dc05-2265.

[7] Murphy HR, Roland JM, Skinner TC, Simmons D, Gurnell E, Morrish NJ, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. Diab Care 2010;33:2514–20. https://doi.org/10.2337/dc10-1113.

[8] Kekäläinen P, Juuti M, Walle T, Laatikainen T. Pregnancy planning in type 1 diabetic women improves glycemic control and pregnancy outcomes. J Matern Neonatal Med 2016;29:2252–8. https://doi.org/10.3109/14767058.2015.1081888.

[9] Wotherspoon AC, Young IS, Patterson CC, McCance DR, Holmes VA. Effect of pregnancy planning on maternal and neonatal outcomes in women with Type 1 diabetes. Diab Med 2017;34:1303–8. https://doi.org/10.1111/dme.13398.

[10] The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450–9.

[11] Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diab Care 1994;17:697–703.

[12] Choudhary P, Geddes J, Freeman JV, Emery CJ, Heller SR, Frier BM. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diab Med 2010;27:666–72. https://doi.org/10.1111/j.1464-5491.2010.03006.x.

[13] Perea V, Orois A, Amor AJ, Jansà M, Vidal M, Gimenez M, et al. Detailed description of a prepregnancy care program and its impact on maternal glucose control, weight gain, and dropouts. Diab Metab Res Rev 2017;33:e2838. https://doi.org/10.1002/dmrr.2838.

[14] Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007;50:2553–61. https://doi.org/10.1007/s00125-007-0820-z.

[15] Dalfrà MG, Sartore G, Di Cianni G, Mello G, Lencioni C, Ottanelli S, et al. Glucose variability in diabetic pregnancy. Diab Technol Ther 2011;13:853–9. https://doi.org/10.1089/dia.2010.0145.

[16] Damm P, Mersebach H, Råstam J, Kaaja R, Hod M, McCance DR, et al. Poor pregnancy outcome in women with type 1 diabetes is predicted by elevated HbA1c and spikes of high glucose values in the third trimester. J Matern Neonatal Med 2014;27:149–54. https://doi.org/10.3109/14767058.2013.806896.

[17] McGrath RT, Glastras SJ, Seeho SK, Scott ES, Fulcher GR, Hocking SL. Association between glycemic variability, HbA1c, and large-for-gestational-age neonates in women with type 1 diabetes. Diab Care 2017;40:e98–e100. https://doi.org/10.2337/dc17-0626.

[18] Jansa M, Quirós C, Giménez M, Vidal M, Galindo M, Conget I. Psychometric analysis of the Spanish and Catalan versions of a questionnaire for hypoglycemia awareness]. Med Clin 2015;144:440–4. https://doi.org/10.1016/j.medcli.2013.11.036.
[19] Standards of medical care in diabetes—2016 : Summary of revisions. Diab Care 2015;39:S4–5. https://doi.org/10.2337/dc16-S003.
[20] EasyGV — Nuffield Department of Primary Care Health Sciences; n.d. https://www.phc.ox.ac.uk/research/technology-outputs/easygv [accessed December 27, 2018].
[21] Perea V, Amor A, Giménez M, Blanco J, Conget I. Glycemic variability measures in a group of subjects with type 1 diabetes and repeated severe and non-severe hypoglycemia. J Diab Sci Technol 2013;7:289–90. https://doi.org/10.1177/193229681300700136.
[22] García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia 2010;53:446–51. https://doi.org/10.1007/s00125-009-1633-z.
[23] Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. Diab Care 2015;38:1592–609. https://doi.org/10.2337/DC15-0102.
[24] Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–77. https://doi.org/10.1016/S0140-6736(18)30297-6.
[25] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. Diab Care 2017;40:1631–40. https://doi.org/10.2337/dc17-1600.
[26] Law GR, Ellison GTH, Secher AL, Damm P, Mathiesen ER, Temple R, et al. Analysis of continuous glucose monitoring in pregnant women with diabetes: distinct temporal patterns of glucose associated with large-for-gestational-age infants. Diab Care 2015;38:1319–25. https://doi.org/10.2337/DC15-0070.
[27] Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet (London, England) 2017;390:2347–59. https://doi.org/10.1016/S0140-6736(17)32400-5.
[28] Tan HK, Little SA, Leelarathna L, Walkinshaw E, Lubina-Solomon A, Hosking J, et al. Low-blood glucose avoidance training improves glycemic variability in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: HypoCOMPaSS trial. Diab Care 2016;39:e56–8. https://doi.org/10.2337/dc15-2431.
[29] Giménez M, Lara M, Jiménez A, Conget I. Glycaemic profile characteristics and frequency of impaired awareness of hypoglycaemia in subjects with T1D and repeated hypoglycaemic events. Acta Diabetol 2009;46:291–3. https://doi.org/10.1007/s00592-008-0085-0.