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SHORT COMMUNICATION

Risk for ketonaemia in type 1 diabetes pregnancies with sensor-augmented pump therapy with predictive low glucose suspend compared with low glucose suspend: a crossover RCT

Katrien Benhalima[1] · Falco van Nes[2] · Annouschka Laenen[3] · Pieter Gillard[1] · Chantal Mathieu[1]

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Abstract

Aims To determine the frequency of ketonaemia in pregnant women with type 1 diabetes treated with a sensor-augmented pump (SAP) in predictive low glucose suspend (PLGS) mode compared with low glucose suspend (LGS) mode.

Methods An open-label crossover pilot RCT in ten women with type 1 diabetes treated with a 640 Medtronic insulin pump, with inclusion between 12–30 weeks of pregnancy. Participants were 1/1 randomly assigned (allocation by statistician using a permuted block size of 2) to either 2 weeks with an SAP in PLGS mode or 2 weeks in LGS mode. After the first 2 weeks, participants were switched to the other mode. Ketones in the participants' serum were measured three times daily (fasting, midday and evening) during the 4 weeks. The primary endpoint was the frequency of blood ketones > 0.6 mmol/l. Participants and healthcare providers were not blinded to group assignment for assessment of outcomes.

Results The median gestational week at inclusion was 12.5 weeks (12.0–15.0), participants had a median age of 31.5 years (24.0–33.0), BMI of 26.6 kg/m^2 (24.5–31.8), baseline HbA_{1c} of 41 mmol/mol (40–43; 5.9% [5.8–6.1]) and baseline time in range (TIR, 3.5–7.8 mmol/l) of 64.6% (55.6–68.7). Comparing the LGS mode with the PLGS mode, insulin suspension time per day was 2.0 h (1.3–2.3) vs 3.5 h (3.3–5.0; $p = 0.002$), ketonaemia > 0.6 mmol/l was 0% vs 0.5% ($p = 1.000$) and no participants had ketonaemia > 1 mmol/l. TIR on LGS was 64.7% (58.0–68.7) vs 61.1% (56.5–67.5) on PLGS ($p = 0.492$), time < 3.5 mmol/l was higher on LGS at 7.5% (4.6–8.3) vs 4.2% (2.4–6.9) on PLGS ($p = 0.014$). Treatment satisfaction and fear for hypoglycaemia were similar whether using LGS or PLGS mode.

Conclusions/interpretation Despite longer time periods with suspended insulin delivery, pregnant women using an SAP in PLGS mode were not at higher risk of developing ketonaemia compared with those in LGS mode. Women with an SAP in PLGS mode had similar TIR with less time in hypoglycaemia.

Trial registration Clinical Trials NCT04292509

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Keywords Ketonaemia · Patient-reported outcomes · Predictive glucose suspension · Pregnancy · Sensor-augmented pump therapy · Type 1 diabetes mellitus

Abbreviations

BHB	β-hydroxybutyrate
DKA	Diabetic ketoacidosis
LBGI	Low blood glucose index
LGS	Low glucose suspend
PLGS	Predictive low glucose suspend
SAP	Sensor-augmented insulin pump
TIR	Time in range

✉ Katrien Benhalima
katrien.benhalima@uzleuven.be

[1] Department of Endocrinology, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium

[2] Department of Medicine, KU Leuven, Leuven, Belgium

[3] Center of Biostatics and Statistical Bioinformatics, KU Leuven, Leuven, Belgium

Research in context

What is already known about this subject?

- Sensor-augmented insulin pump (SAP) therapy with predictive low glucose suspend (PLGS) technology decreases time spent in hypoglycaemia, without an increase in HbA_{1c}
- An SAP can be used in two modes of actions: low glucose suspend (LGS) or PLGS

What is the key question?

- Is there an increased risk for ketonaemia with PLGS compared with LGS in pregnant women with type 1 diabetes?

What are the new findings?

- This pilot RCT suggests that using an SAP in PLGS mode does not increase the risk of ketonaemia in women with type 1 diabetes between 12–30 weeks of pregnancy, despite the significantly increased suspension time of insulin compared with LGS mode
- Participants using an SAP in PLGS mode achieved similar time in range with less time in hypoglycaemia compared with LGS mode
- There were no significant differences in glycaemic variability, treatment satisfaction or fear for hypoglycaemia when using either mode of action

How might this impact on clinical practice in the foreseeable future?

- SAP therapy with PLGS might be a safe alternative to LGS in pregnant women with type 1 diabetes, without increased risk for significant ketonaemia and with the advantage of less time in hypoglycaemia compared with LGS

Introduction

As tight glycaemic control improves pregnancy outcomes in women with type 1 diabetes mellitus, sensor-augmented insulin pump (SAP) therapy is frequently used in pregnancy [1]. SAP therapy can be used in two different modes of actions. Low glucose suspend (LGS) mode suspends insulin delivery up to 2 h once the preset hypoglycaemic threshold is reached. In contrast, predictive low glucose suspend (PLGS) mode leads to insulin delivery suspension when the algorithm predicts hypoglycaemia within the next 30 min, preventing hypoglycaemic events.

Pregnancy predisposes the mother to accelerated starvation by switching from the use of hepatic glycogen to lipolysis during fasting, leading to an increased risk for ketonaemia [2]. The increased time of insulin delivery suspension associated with SAP therapy could theoretically lead to increased ketonaemia in pregnancy. Moreover, it remains unclear whether there is an increased risk for ketonaemia with PLGS compared with LGS. We aimed to determine the frequency of ketonaemia and glycaemic control between PLGS and LGS in pregnant women with type 1 diabetes.

Methods

Research design The ROKSANA study was a monocentric open-label crossover pilot RCT. The protocol (NCT04292509) was approved by the Institutional Review Board of UZ Leuven.

Women treated with a 640G Medtronic insulin pump and Guardian 3 sensor (Medtronic, USA) were offered inclusion between 12 and 30 weeks of pregnancy. Women needed to have been diagnosed with type 1 diabetes > 1 year before pregnancy, be 18–45 years, with a singleton pregnancy and baseline $HbA_{1c} \leq 10\%$. We aimed for ten participants to complete the study.

Participants were 1/1 randomly assigned to 2 weeks with PLGS or 2 weeks with LGS. After the first 2 weeks, participants were switched to the other mode. The randomisation was performed by SAS software (version 9.4 of the SAS System for Windows, SAS Institute, USA) using a permuted block size of 2. Participants measured β-hydroxybutyrate (BHB) in their serum three times daily (fasting, around 2 pm [1–3 pm] and around 10 pm [9–11 pm]) with the Freestyle Abbott meter (Abbott, USA). Participants were asked to record daily the concentration of blood ketones, time of the ketone measurement and time of the last meal before the ketone measurement.

Table 1 Baseline characteristics of participants ($N = 10$)

Characteristic	Value
Gestational age at inclusion (weeks)	12.5 (12.0–15.0)
Age (years)	31.5 (24.0–33.0)
Ethnicity	
White	9 (90)
North African	1 (10)
BMI (kg/m^2)	26.6 (24.5–31.8)
Baseline HbA_{1c} (mmol/mol)	41 (40–43)
Baseline HbA_{1c} (%)	5.9 (5.8–6.1)
Baseline TIR (%)	64.6 (55.6–68.7)
Duration of diabetes (years)	20.5 (14.0–23.0)
Total daily insulin dose (U/day)	39.9 (31.8–46.7)
Primiparous	8 (80)

Data are n (%) or median (IQR)

Baseline indicates before randomisation

Participants were followed up every 2 weeks in line with normal routine, with measurement of HbA_{1c}, BP and weight. BMI was calculated as kg/m^2. HbA_{1c} was analysed using a Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh, Japan).

Participants completed several questionnaires at baseline and after the switch to either mode. These included the Hypoglycaemia Fear Survey II (HFS-II) [3], quality of life (SF-36) questionnaire [4], 20-item Center for Epidemiologic Studies-Depression (CES-D) questionnaire (score ≥ 16 suggestive for clinical depression) [5], Problem Areas in Diabetes-short form (PAID-5; which assesses fear, depressed mood and the demands of living with diabetes [6]), Diabetes Treatment Satisfaction Questionnaires (DTSQ status and DTSQ change) [7] and the Frequency Food questionnaire (FFQ) validated for the Belgian population [8].

The primary endpoint was the frequency of blood ketones > 0.6 mmol/l (according to the indication of the meter for elevated ketones). Secondary outcomes were mean blood ketone concentration, mean time of suspension of insulin delivery, hospitalisation due to ketonaemia, time in range (TIR; 3.5–7.8 mmol/l), time > 7.8 mmol/l, > 10 mmol/, < 3.5 mmol/l, < 3.0 mmol/l, < 2.8 mmol/l and low blood glucose index (LBGI) [9]. To evaluate glycaemic variability, CV % and mean amplitude of glucose excursions were measured [10]. Additional outcomes were HbA_{1c}, continuous glucose monitoring compliance, total insulin dose and patient-reported outcome measures.

Statistical analyses Descriptive statistics are presented as median with IQR for continuous variables (not normally distributed) and as frequencies with percentages for categorical variables. Comparisons were performed by a Wilcoxon signed rank test for continuous/ordinal variables and by the McNemar test for binary variables.

Results

Twelve participants were recruited. Of these, one withdrew before randomisation because of a miscarriage, and one withdrew after randomisation due to lack of compliance with the ketone measurements. Ten participants completed the study. Median gestational age at inclusion was 12.5 weeks (12.0–15.0), eight women were included in the second trimester and two in the third trimester (Table 1). All women were already using SAP therapy before pregnancy. Within 1 year before pregnancy, one participant had a history of mild diabetic retinopathy, one had a history of microalbuminuria, two had a history of a severe hypoglycaemia and none had a history of diabetic ketoacidosis (DKA).

No difference was found in frequency of ketonaemia > 0.6 mmol/l between LGS and PLGS (0% [0] vs 0.5% [2], $p = 1.000$, based on a total number of ketone measurements during the 2-week observation period of 357 and 378, respectively), and no participants had ketonaemia > 1 mmol/l (Table 2). Median ketonaemia levels at the different time points during the day were < 0.1 mmol/l during both mode of actions (Table 2). Two episodes of limited increased ketonaemia occurred on the same day in one participant on PLGS who had eaten less the day before and had vomited once (ketonaemia of 0.8 mmol/l fasting and 0.7 mmol/l in the afternoon). There were no significant differences in the time of the day when ketones were measured, nor in the time between the last meal and ketone measurement when using either mode of action (Table 2). Median daily carbohydrate intake was similar, around 185 g between both modes of actions (Table 2). Daily insulin suspension time was significantly lower during LGS (2.0 h, 1.3–2.3 h) compared with PLGS (3.5 h, 3.3–5.0 h; $p = 0.002$). Women on LGS had a similar TIR of 64.7% (58.0–68.7%) compared with women on PLGS with 61.1% (56.5–67.5%, $p = 0.492$), but they spent more time < 3.5 mmol/l (7.5% [4.6–8.3%] vs 4.2% [2.4–6.9%], $p = 0.014$) and had a higher LBGI of 2.8 (1.8–3.5) vs 1.9 (1.4–2.6, $p = 0.019$) (Table 2). Time < 3.0 mmol/l and time < 2.8 mmol/l were also lower when using PLGS compared with LGS, but this did not reach statistical significance. No episodes of severe hypoglycaemia occurred. Glycaemic variability was similar between both modes of actions (Table 2). There were no hospitalisations due to ketonaemia or DKA. There were no significant differences in treatment satisfaction, fear for hypoglycaemia, symptoms of depression or quality of life when using either mode of action (Table 2). Pregnancy outcomes

Table 2 Ketonaemia, glycaemic outcomes and treatment satisfaction

Variable	LGS	PLGS	*p* value
Insulin suspension time per day (h)	2.0 (1.3–2.3)	3.5 (3.3–5.0)	0.002
Insulin suspension time over a 2-week period (h)	28.3 (117.9–32.0)	48.8 (45.8–70.0)	0.002
Number of stops of insulin suspension per day	1.9 (1.3–2.2)	4.0 (3.4–4.3)	0.002
Total daily insulin dose (U/day)	41.4 (32.4–56.9)	41.7 (36.6–48.4)	0.432
CGM compliance (>80% of time)	8 (80)	8 (80)	1.000
Total energy intake (kJ)	6225.8 (5271.8–8920.3)	5790.6 (4778.1–8732.0)	0.547
Total energy intake (kcal)	1488 (1260–2132)	1384 (1142–2087)	
Total carbohydrate intake (g/day)	187.8 (177.8–280.8)	184.1 (155.8–268.1)	0.383
Total carbohydrates relative score (E %)[a]	53.4 (50.2–55.6)	52.1 (50.7–53.7)	0.109
Total protein intake (g/day)	78.0 (45.6–85.8)	62.6 (47.7–83.6)	0.844
Total protein relative score (E %)[a]	16.7 (15.3–19.5)	16.2 (14.2–18.3)	0.742
Total fat intake (g/day)	51.5 (35.5–72.9)	48.3 (39.4–73.9)	0.383
Total fat relative score (E %)[a]	29.7 (26.3–31.1)	30.6 (28.5–33.8)	0.016
Total ketonaemia per day	0.08 (0.06–0.09)	0.08 (0.07–0.11)	0.084
Fasting ketonaemia per day (mmol/l)	0.08 (0.05–0.10)	0.07 (0.06–0.11)	0.432
Midday ketonaemia per day (mmol/l)	0.07 (0.04–0.09)	0.09 (0.08–0.10)	0.002
Evening ketonaemia per day (mmol/l)	0.08 (0.06–0.11)	0.08 (0.06–0.11)	1.000
Frequency of ketonaemia > 0.6 mmol/l[b]	0 (0)	2 (0.5)	1.000
Frequency of ketonaemia > 1 mmol/l[b]	0 (0)	0 (0)	–
Time of measurement, fasting ketonaemia	08:27 (08:14–09:03)	08:34 (08:00–09:11)	0.846
Time of measurement, midday ketonaemia	13:49 (13:45–14:33)	14:10 (13:55–14:38)	0.232
Time of measurement, evening ketonaemia	21:36 (20:58–22:05)	22:16 (21:28–22:23)	0.492
Time since last meal before fasting ketonaemia (h)	14.2 (12.9–15.2)	14.1 (13.3–14.8)	0.469
Time since last meal before midday ketonaemia (h)	2.4 (1.2–2.6)	2.0 (1.8–3.8)	0.578
Time since last meal before evening ketonaemia (h)	3.5 (3.3–6.4)	3.9 (3.5–4.4)	0.641
TIR (%)	64.7 (58.0–68.7)	61.1 (56.5–67.5)	0.492
Median sensor calculated glucose (mmol/l)	6.6 (6.3–7.1)	7.0 (6.7–7.2)	0.070
HbA_{1c} (mmol/mol)[c]	42 (40–43)	42 (39–42)	0.437
HbA_{1c} (%)[c]	6.0 (5.8–6.1)	6.0 (5.7–6.0)	0.437
Time > 7.8 mmol/l (%)	30.1 (23.6–35.2)	33.3 (28.6–36.6)	0.193
Time > 10 mmol/l (%)	10.3 (6.7–13.7)	14.4 (10.5–16.6)	0.275
Time < 3.5 mmol/l (%)	7.5 (4.6–8.3)	4.2 (2.4–6.9)	0.014
Time < 3.0 mmol/l (%)	3.0 (2.3–3.8)	1.8 (1.1–4.2)	0.164
Time < 2.8 mmol/l (%)	2.1 (1.4–2.7)	1.1 (0.8–3.1)	0.232
LBGI	2.8 (1.8–3.5)	1.9 (1.4–2.6)	0.019
CV (%)	37.2 (35.3–39.7)	35.1 (32.9–39.0)	0.310
Mean amplitude of glycaemic excursions (mmol/l)	6.7 (6.0–7.5)	6.9 (6.4–7.6)	1.000
DTSQs satisfaction	29.5 (26.0–34.0)	32.0 (27.0–33.0)	0.656
DTSQs hypoglycaemia	5.0 (4.0–6.0)	6.0 (5.0–6.0)	0.500
DTSQc satisfaction	0 (0–0)	1.0 (0–2.0)	1.000
DTSQc hypoglycaemia	0 (0–1.0)	0 (−1.0–0)	0.562
HFS-II	20.0 (17.0–22.0)	22.0 (19.0–23.0)	0.547
PAID-5	2.5 (1.0–5.0)	3.0 (1.0–5.0)	1.000
CES-D	7.0 (4.0–9.0)	12.0 (6.0–24.0)	0.125
SF-36			
Physical functioning	70.0 (60.0–75.0)	70.0 (45.0–85.0)	0.875
Limitations due to physical health	65.6 (21.9–81.2)	75.0 (50.0–87.5)	0.687
Limitations due to emotional problems	91.7 (66.7–100.0)	95.8 (70.8–100.0)	0.625
Fatigue	62.5 (53.1–68.7)	62.5 (56.2–78.1)	0.883
Emotional well-being	82.5 (77.5–87.5)	75.0 (67.5–85.0)	0.172

Table 2 (continued)

Variable	LGS	PLGS	*p* value
Social functioning	87.5 (75.0–100.0)	93.7 (81.2–100.0)	1.000
Pain	82.0 (74.0–92.0)	79.0 (51.5–100.0)	0.625
General health	74.5 (64.5–87.0)	67.0 (64.5–74.5)	0.406

Data are presented as n (%) or median (IQR). Data on HbA_{1c}, insulin dose, dietary intake and the different questionnaires were collected at the end of each 2-week period of LGS and PLGS. Data on the ketone measurements and CGM data for LGS and PLGS are presented for the 2-week observation period

[a] E % is the relative intake of carbohydrates, fat or protein, expressed as energy percentage of the total amounts of macronutrients intake

[b] Frequency of ketonaemia based on the total number of ketone measurements over the 2-week observation period of 357 and 378 for LGS and PLGS, respectively

[c] HbA1c after 2 weeks of LGS or PLGS mode, respectively

CES-D, the 20-item Center for Epidemiologic Studies-Depression questionnaire; CGM, continuous glucose monitoring; DTSQs, the Diabetes Treatment Satisfaction Questionnaire (status); DTSQc, the Diabetes Treatment Satisfaction Questionnaire (change); HFS-II: the Hypoglycaemia Fear Survey II; PAID-5, the Problem Areas in Diabetes-short form; SF-36, the SF-36 quality of life questionnaire

are reported in electronic supplementary material (ESM) Table 1.

Discussion

Our data suggest that PLGS does not increase the risk of ketonaemia in pregnant women with type 1 diabetes despite the significantly increased suspension time of insulin compared with LGS. In addition, participants achieved similar TIR with less time in hypoglycaemia. Moreover, there were no significant differences in glycaemic variability, treatment satisfaction or fear for hypoglycaemia when using either mode of action.

SAP therapy with PLGS technology decreases time spent in hypoglycaemia, without an increase in HbA_{1c} [11]. However, the increased time of insulin delivery suspension with insulin suspend technology could theoretically lead to increased ketonaemia in pregnancy. To our knowledge, this study is the first RCT to assess the risk for increased ketonaemia when using SAP therapy in pregnancy. We found no clinically significant ketonaemia (> 1 mmol/l) with either LGS or PLGS. This suggests that both modes of actions are safe to use in pregnancy.

There is no debate that DKA in pregnancy is an urgent complication which can compromise both fetus and mother [2]. However, studies have shown conflicting results as to whether there is an association between elevated maternal ketone levels, adverse pregnancy outcomes and their impact on childhood IQ [2, 12]. Larger studies are needed to determine the impact of maternal ketones on pregnancy outcomes and offspring's IQ.

It is currently also not known what amount of carbohydrate intake in pregnancy is sufficient to prevent ketone levels. The median daily carbohydrate intake in our study was around 185 g. In general, a minimum daily intake of 175 g carbohydrate is recommended during pregnancy but this is based on very limited evidence [2]. A recent study of women with gestational diabetes mellitus demonstrated that a carbohydrate diet of 165 g per day does not result in increased fasting BHB levels [13].

A strength of this study includes the randomised crossover design. We chose to measure serum BHB instead of ketones in urine since this is more reliable and easy-to-perform. Urine testing for ketones has a significant rate of false-positive and false-negative results [14]. We did not restrict participants' dietary habits, exercise or travel, mimicking real-life in the study as much as possible.

There were some limitations to this study. The relatively short observation period and small sample size may have been insufficient to evaluate differences in ketonaemia between LGS and PLGS. On the other hand, multiple daily ketone measurements for a longer time period would be difficult to accomplish. We could not perform a formal power calculation due to lack of data on the differences in ketonaemia between LGS and PLGS in pregnancy, and we therefore chose a pragmatic sample size. Most participants were included in the second trimester of pregnancy, although the risk for ketonaemia might be higher later in pregnancy. Participants had, in general, well controlled diabetes, which might have minimised the risk for significant ketonaemia. We expect limited bias in patient selection, since all women eligible for the study agreed to participate. To account for two dropouts, we continued recruitment until ten participants completed the study.

In conclusion, SAP therapy with PLGS might be a safe alternative to LGS in pregnancy, without increased risk for significant ketonaemia. However, larger studies are needed to further explore the risk for ketonaemia with SAP therapy in pregnancy.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05589-y.

Author contributions KB, CM and PG conceived the study. FV did the data collection. AL performed the statistical analysis. KB did the literature review and wrote the first draft. All authors substantially contributed to conception and design, acquisition of data, or analysis and interpretation of data. All authors revised it critically for important intellectual content and approved the final version to be published. The corresponding author KB had full access to all the data in the study and had final responsibility for the contents of the article and the decision to submit for publication. KB is the guarantor of the study.

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Data availability All data generated or analysed during this study are included in this published article (and its supplementary information files).

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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