Received: 17 April 2021 | Accepted: 11 January 2022

DOI: 10.1111/dme.14789

DIABETIC Medicine

RESEARCH ARTICLE

Impaired awareness of hypoglycaemia in women with type 1 diabetes in pregnancy: Hypoglycaemia fear, glycaemic and pregnancy outcomes

Jasmine Bahrami[1,2] | **George Tomlinson**[1,3] | **Helen R. Murphy**[4,5] | **Denice S. Feig**[1,2,6] | **the CONCEPTT Collaborative Group†**

[1]Department of Medicine, University of Toronto, Toronto, Canada

[2]Leadership Sinai Centre for Diabetes, Mt Sinai Hospital, Sinai Health System, Toronto, Ontario, Canada

[3]University Health Network, Toronto, Ontario, Canada

[4]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[5]Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK

[6]Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada

Correspondence
Denice S. Feig, Department of Medicine, University of Toronto, Toronto, Canada.
Email: d.feig@utoronto.ca

Present address
Jasmine Bahrami, Markham Stouffville Hospital, Markham, Ontario, Canada

Funding information
CONCEPTT was funded by JDRF grant 17-2011-533 and grants under the JDRF Canadian Clinical Trial Network, a public–private partnership including JDRF and FedDev Ontario and supported by JDRF no. 80-2010-585. Medtronic supplied the CGM sensors and CGM systems at a reduced cost. HRM conducts independent research supported by the National Institute for Health Research (Career Development Fellowship CDF-2013-06-035). GT, HRM, and DSF report grants from JDRF. HRM is supported by Tommy's charity. DSF reports grants from the Canadian Institutes of Health Research. The views expressed in this publication are those

Abstract

Aims: To examine maternal fear of hypoglycaemia, glycaemia and pregnancy outcomes in women with impaired and normal awareness of hypoglycaemia.

Methods: A pre-planned sub-study of 214 pregnant women with type 1 diabetes who participated in the CONCEPTT trial. Participants completed hypoglycaemia fear surveys (HFS-II) at baseline. Logistic regression and Poisson regression analyses were used to obtain an adjusted estimate for the rate ratio relating awareness to the number of severe hypoglycaemic episodes, and for several neonatal outcomes in relation to the total HFS-II score. The role of continuous glucose monitoring (CGM) use was examined.

Results: Overall, 30% of participants reported impaired awareness of hypoglycaemia ($n = 64$). Women with impaired awareness of hypoglycaemia had more episodes of severe hypoglycaemia (mean 0.44 vs. 0.08, $p < 0.001$) (12–34 weeks gestation) and scored higher on the HFS-II scale (43.7 vs. 36.0, p 0.008), indicating more fear of hypoglycaemia. They spent more time below range (CGM <3.5 mmol/L) and exhibited more glycaemic variability at 12 weeks gestation. Higher overall HFS-II scores were associated with a higher risk of maternal severe hypoglycaemia episodes (Rate Ratio 1.78, 95% CI 1.39–2.27). Women with impaired awareness of hypoglycaemia had less maternal weight gain but there

†See Supplementary Material.

of the authors and not necessarily those of the National Institute for Health Research or the UK Department of Health. The study sponsor/funder was not involved in the design of the study, the collection, analysis, interpretation of the data or in the writing of the report.

were no differences in neonatal outcomes between women with impaired awareness of hypoglycaemia and normal hypoglycaemia awareness. Higher HFS-II scores were associated with more nephropathy (Odds Ratio 1.91, 95% CI 1.06–3.4). CGM use after 12 weeks was not associated with the number of episodes of severe hypoglycaemia (RR 0.75, 95% CI 0.49–1.15; $p = 0.18$).

Conclusions: In pregnant women with type 1 diabetes, impaired awareness of hypoglycaemia is associated with more maternal severe hypoglycaemia episodes and more fear of hypoglycaemia. Having impaired awareness of hypoglycaemia and/or fear of hypoglycaemia should alert clinicians to this increased risk. Reassuringly, there was no increase in adverse neonatal outcomes.

KEYWORDS

diabetes mellitus, diabetes mellitus type 1, hypoglycaemia, pregnancy, pregnancy complications, pregnancy in diabetes, pregnancy outcomes, severe hypoglycaemia

1 | INTRODUCTION

Pregnant women with type 1 diabetes are at increased risk of maternal and neonatal complications.[1–3] Improving glycaemia before and during pregnancy reduces the risk of many complications, including congenital malformations, preeclampsia and preterm delivery.[4–6] However, striving for tight pregnancy glucose targets is associated with an increased frequency of hypoglycaemic episodes, including severe hypoglycaemia.[7,8] Severe hypoglycaemia is defined as any hypoglycaemic episode requiring the assistance of a third party.[9] Most severe hypoglycaemia episodes occur in early pregnancy, with the highest incidence between 8 and 16 weeks of gestation.[4,10] Severe hypoglycaemia is associated with an increased risk of seizures, hospitalizations and maternal death.[6,11] Risk factors for severe hypoglycaemia during pregnancy include the previous history of severe hypoglycaemia, longer duration of diabetes and higher total daily insulin use.[12] Of note, these studies were older, where insulin analogues were not used and there was no continuous glucose monitoring (CGM) available. Impaired awareness of hypoglycaemia is another important risk factor for severe hypoglycaemia.[4] Impaired awareness of hypoglycaemia predisposes non-pregnant individuals with type 1 diabetes to a sixfold increase in the frequency of severe hypoglycaemia, much of which occurs at home during waking hours.[13]

Data on impaired awareness of hypoglycaemia during pregnancy is lacking, but several factors may contribute to impaired awareness of hypoglycaemia, including striving for the tight pregnancy glycaemic targets, as well as the reduction in counter-regulatory hormones secreted in response to hypoglycaemia seen during pregnancy.[14,15] Furthermore, frequent episodes of hypoglycaemia, often seen during pregnancy, also predisposes to impaired awareness of hypoglycaemia, which in turn leads to an increased risk of severe hypoglycaemia.[16,17]

To date, there is a paucity of data on maternal and neonatal outcomes in pregnant women with impaired awareness of hypoglycaemia. We hypothesised that women with impaired awareness of hypoglycaemia not only have an increased risk of severe hypoglycaemia, but they may spend more time in the hypoglycaemic range. On the contrary,

What is already known?

Women with impaired hypoglycaemia awareness are at increased risk of severe hypoglycaemia. Little is known about impaired hypoglycaemia awareness during pregnancy.

What this study has found?

Impaired hypoglycaemia awareness was associated with more episodes of severe hypoglycaemia and more fear of hypoglycaemia throughout pregnancy. Women spent more time below the glycaemic target range and showed more glycaemic variability in the first trimester. There were no differences in neonatal outcomes.

What are the clinical implications of the study?

Pregnant women with impaired hypoglycaemia awareness and their caregivers should be cognizant of their increased risk of severe hypoglycaemia episodes and increased fear of hypoglycaemia. Reassuringly, neonatal outcomes were comparable.

they may have an increased fear of hypoglycaemia and may keep their blood sugars higher; therefore, leading to worse pregnancy outcomes. A prospective cohort study of pregnant women with type 1 diabetes suggested that infants of women with impaired awareness of hypoglycaemia were at increased risk of neonatal respiratory distress syndrome.[11] Maternal outcomes were otherwise comparable between women with impaired awareness of hypoglycaemia and those with normal awareness of hypoglycaemia. However, this study relied on self-reported blood glucose data from participants and did not include validated patient-reported outcomes or CGM data.

The continuous glucose monitoring in women with type 1 diabetes in pregnancy trial[1] (CONCEPTT) was a trial that randomised women to either CGM or capillary glucose monitoring. It included similar proportions of women using insulin pumps and MDI and reported a similar incidence of severe hypoglycaemia after 12 weeks in women randomised to CGM vs standard glucose monitoring. However, a detailed analysis of the impact of impaired awareness of hypoglycaemia was not performed. The aim of this pre-planned sub-study was to examine maternal fear of hypoglycaemia, CGM glucose profiles and pregnancy outcomes in women with impaired and normal awareness of hypoglycaemia. We hypothesised that women with impaired awareness of hypoglycaemia would have poorer neonatal outcomes compared to women with normal awareness of hypoglycaemia.

2 | METHODS

2.1 | Study design and population

We included 214 pregnant women with type 1 diabetes who participated in the CONCEPTT trial. A detailed description of the CONCEPTT trial has been published elsewhere.[1,18] In brief, the CONCEPTT trial was an international, multicentre, randomised trial examining maternal and neonatal outcomes using real-time CGM in women with type 1 diabetes who were pregnant or planning pregnancy. Eligible participants were randomised to the use of real-time CGM or standard care which consisted of capillary glucose monitoring. Maternal and neonatal glycaemic and health outcomes were collected, including but not limited to maternal episodes of severe hypoglycaemia, HbA1c (at randomisation [approximately 12 weeks], 24 weeks, 34 weeks), CGM measures including time in range, time below range and glycaemic variability taken at baseline (approximately 12 weeks), 24 and 34 weeks in both groups, as well as neonatal hypoglycaemia, birth weight and NICU admissions. This pre-planned sub-study includes analyses of data from the CONCEPTT trial. Informed consent was obtained for the main trial. Ethics approval for this study was obtained from the Mount Sinai Research Ethics Board.

2.2 | Definitions and outcome measures

Women enrolled in the CONCEPTT trial were asked about hypoglycaemia awareness symptoms at randomisation and ranked one of 'Always aware' 'Sometimes aware' or 'Never aware'. Participants who chose either 'Sometimes aware' or 'Never aware' were considered to have impaired awareness of hypoglycaemia, as only six reported 'Never aware'. Those who indicated they were 'Always aware' were considered to have normal hypoglycaemia awareness. In addition, participants were asked to complete the hypoglycaemia fear survey (HFS-II) questionnaire at baseline. The HFS-II questionnaire is a well-described and validated tool used to study the fear of hypoglycaemia in patients with diabetes.[19,20] The 33-part questionnaire consists of three subscales: Behaviour-avoidance subscale and Behaviour-maintain high blood glucose subscale and Worry subscale, comprising 18, 10 and 3 questions each, respectively. Questions are rated on a 5-point Likert scale from 0 (never) to 4 (always), with higher scores representing increased fear of hypoglycaemia. The maximum possible score on the HFS-II scale is 132. If a participant chose not to answer a question, the total score was prorated as a percentage of questions answered.

Our primary research question was to determine whether maternal glycaemic and neonatal outcomes differed in women with impaired awareness of hypoglycaemia compared to women with normal hypoglycaemia awareness. Maternal glycaemic outcomes included a number of episodes of severe hypoglycaemia, percentage of time spent below range (<3.5 mmol/L), time spent in range (3.5–7.8 mmol/L) and time spent above range (>7.8 mmol/L) using CGM, change in HbA1c, as well as glycaemic variability measures (glucose standard deviation and glucose coefficient of variation) at baseline, 24 and 34 weeks gestation. A severe hypoglycaemic episode was defined as an episode of hypoglycaemia requiring assistance from a third party.

Maternal health outcomes included worsening chronic hypertension, preeclampsia, gestational hypertension, maternal weight gain, pregnancy loss (including termination, miscarriage prior to 20 weeks and stillbirth) and worsening of diabetes complications (retinopathy, nephropathy, neuropathy). Neonatal outcomes included congenital anomalies, preterm birth, small for gestational age, large for gestational age (LGA), birth injury, shoulder dystocia, neonatal hypoglycaemia, hyperbilirubinemia, respiratory distress syndrome (RDS), high-level neonatal

care, and infant length of hospital stay. If there were differences found at baseline, we planned to adjust analyses for these factors.

Clinical and demographic variables were summarised according to hypoglycaemia awareness groups using means and standard deviations for continuous variables and counts and percentages for categorical variables. Groups were compared using t-tests, chi-squared tests or Fisher's exact tests, as appropriate. A similar approach was taken for maternal, neonatal and glycaemic outcomes of pregnancy, but here we also carried out some additional analyses. Regression models were used to obtain an adjusted estimate for the rate ratio relating awareness to the number of severe hypoglycaemic episodes, and for several neonatal outcomes in relation to the total HFS-II score. A Poisson regression model was used to compare the rates of severe hypoglycaemic episodes over the duration of the pregnancy between groups. The dependence of outcomes on HFS-II scores was assessed using Poisson regression (for the number of severe hypoglycaemic episodes) and logistic regression (for binary outcomes with at least 10 occurrences). Where there were sufficient events to support additional covariates in these models, the analyses included randomised intervention group, pre-pregnancy weight and a composite measure of prenatal care, use of vitamins or folic acid, as these either appeared different at baseline in the IAH groups or, in the case of treatment, could have a direct effect on the outcome. Correlations were estimated between HFS-II scores and several CGM measures of glycaemic control as defined by the international consensus group: time above, below and in target, and two measures of glycaemic variability (standard deviation and coefficient of variation).

3 | RESULTS

3.1 | Demographics of participants

Overall, 64/214 (30%) of participants reported impaired awareness of hypoglycaemia (Table 1). There were no differences in maternal age, duration of diabetes, smoking, education levels, height, gestational age at randomization or baseline diabetes-related complications between women who reported impaired awareness of hypoglycaemia and those with normal hypoglycaemia awareness (Table 1). Participants with impaired awareness of hypoglycaemia had a statistically significantly higher body mass index (BMI) at baseline. There were no significant differences in insulin delivery method or the total daily dose of insulin between the two groups. Women with impaired awareness of hypoglycaemia were less likely to use preconception folic acid and preconception prenatal vitamins (Table 1). More women with impaired awareness of hypoglycaemia had an episode of severe hypoglycaemia prior to pregnancy and during early pregnancy prior to randomisation, compared to women with normal hypoglycaemia awareness (Table 2).

3.2 | Glycaemic outcomes

There were no differences in HbA1c at entry, 24 or 34 weeks GA between impaired awareness of hypoglycaemia vs normal hypoglycaemia awareness (Table 2). There were differences in continuous glucose measures between women with impaired awareness of hypoglycaemia vs normal hypoglycaemia awareness at baseline (approximately 12 weeks gestation). Women with impaired awareness of hypoglycaemia spent more time below the glycaemic target range (<3.5 mmol/L), (10.3% vs. 8.0%, $p = 0.034$) (Table 2 and Figure 1), and had more glycaemic variability as shown by glucose standard deviation and coefficient of variation (Table 2). By 24 and 34 weeks gestation, there were no longer any between-group differences in continuous glucose measures (Table 2). Time spent in and above the target range was comparable between the two groups at all time points (12, 24 and 34 weeks) (Figure 1).

Women with impaired awareness of hypoglycaemia had more episodes of severe hypoglycaemia during pregnancy, both before study entry (approximately 12 weeks gestation) and during the remainder of the pregnancy (Table 2). Both the mean number of episodes (0.08 vs. 0.44 per woman, $p < 0.001$) and the number of episodes per woman were significantly higher in the impaired awareness of the hypoglycaemia group post-study entry (Table 2). The estimated relative increase was larger after adjusting for specified baseline covariates (rate ratio = 7.5; 95% CI: 4.6–12.7; $p < 0.001$). In this model, the use of CGM was not strongly associated with the number of episodes of severe hypoglycaemia (RR 0.75, 95%CI 0.49–1.15; $p = 0.18$). The increase in the rate of episodes of severe hypoglycaemia with impaired awareness of hypoglycaemia was present in both users and non-users of CGM (results not shown).

3.3 | Obstetric maternal and neonatal outcomes

Women with impaired awareness of hypoglycaemia had less gestational weight gain compared to women with normal hypoglycaemia awareness (12.4 ± 4.9 kg vs. 14.2 ± 5.9 kg [$p = 0.043$]) (Table 3). There were no between-group differences in birth status (termination, pregnancy loss prior to 20 weeks, or stillbirth) or hypertensive disorders of pregnancy, including preeclampsia,

TABLE 1 Baseline characteristics of pregnant participants in CONCEPTT by hypoglycaemia awareness ($N = 214$ unless specified)

	Normal awareness of hypoglycaemia	Impaired awareness of hypoglycaemia	*p* value
N (unless specified below)	150	64	
Randomised to continuous glucose monitoring	74 (49)	33 (52)	0.881
Maternal age (years)	31.5 ± 4.8	31.2 ± 4.5	0.664
Ethnic background			
European/Mediterranean	127 (85)	57 (89)	0.527
Other	23 (15)	7 (11)	
Gestational age at randomization (weeks)	10.8 ± 2.0	10.7 ± 2.5	0.986
Primiparous	56 (37)	28(45)	0.468
Height in the first trimester in cm	165.6 ± 6.3	165.3 ± 6.9	0.789
Weight in the first trimester in kg	69.5 ± 12.8	73.0 ± 14.7	0.089
Body Mass Index (kg/m^2)	25.3±4.1	26.7 ± 5.2	0.040
Duration of diabetes in years	16.8 ± 7.5	16.6 ± 8.2	0.857
Smokers	14 (9.3)	7 (11)	0.912
Education level			
Secondary school or less	36 (24)	14 (22)	0.873
Post-secondary school	114 (76)	50 (78)	
Folic acid use			
Started before conception	**82 (63)** ***N* = 131**	**27 (45)** ***N* = 60**	**0.034**
Prenatal vitamin use			
Started before conception	**48 (46)** ***N* = 104**	**13 (27)** ***N* = 49**	**0.033**
Insulin delivery method			
Insulin pump	74 (49)	24 (37)	0.15
Multiple daily injection	76 (51)	40 (63)	
Total insulin dose (units/kg/day)	0.74 ± 0.27 *N* = 149	0.70 ± 0.32 *N* = 64	0.376
Diabetic complications			
Retinopathy	38 (25)	13 (20)	0.539
Nephropathy	4 (2.7)	4 (6.2)	0.383
Neuropathy	6 (4.0)	1 (1.6)	0.618

Note: Results shown are mean ± SD or *n* (%). Bold indicate statistically significant values.

gestational hypertension and worsening chronic hypertension (Table 3). Furthermore, there were no differences in any of the neonatal outcomes studied based on hypoglycaemia awareness status.

3.4 | Patient-reported outcomes

Women with impaired awareness of hypoglycaemia scored higher overall on the HFS-II questionnaire, and specifically on the worry scale of the HFS-II questionnaire (Table 4), indicating more fear of hypoglycaemia and more worry about hypoglycaemia. There were no differences in the HFS-II Behaviour sub-scale between women with impaired awareness of hypoglycaemia vs normal hypoglycaemia awareness (Table 4).

Higher overall HFS-II scores were associated with a higher rate of maternal severe hypoglycaemia episodes (rate ratio 1.78 per 20 points, 95% CI 1.39–2.27) (Table 5), a higher incidence of diabetic nephropathy (OR 1.9, 95% CI 1.1–3.4) and a lower incidence of neonatal hypoglycaemia (OR 0.68, 95% CI 0.45–1.00) (Table 5). There was a weak positive association between time spent below range and HFS total score (Figure S1) at baseline (12 weeks) but no

TABLE 2 Glycaemic outcomes of pregnant participants in CONCEPTT by hypoglycaemia awareness ($N = 214$ unless specified)

	Normal hypoglycaemia awareness $N = 150$	**Impaired awareness of hypoglycaemia $N = 64$**	***p* value**
Any episode of severe hypoglycaemia in the year prior to entry pregnancy	**7 (4.7)**	**13 (20)**	**0.001**
Any episode of severe hypoglycaemia during pregnancy prior to study entry	**4 (2.7)**	**7 (11)**	**0.030**
Severe hypoglycaemia during pregnancy after entry	$N = 146$	$N = 61$	
0 episodes	**137 (94)**	**47 (77)**	**0.003**
1 episode	**7 (4.8)**	**8 (13)**	
2 episodes	**1 (0.7)**	**2 (3.3)**	
3+ episodes	**1 (0.7)**	**4 (6.6)**	
Number of episodes[a]	**0.08 ± 0.36**	**0.44 ± 1.06**	**<0.001**
HbA1c at entry	$N = 136$	$N = 59$	
%	6.9 ± 0.7	6.9 ± 0.7	0.923
mmol/mol	52 ± 7	52 ± 7	
HbA1c at 24 weeks	$N = 133$	$N = 57$	
%	6.3 ± 0.6	6.3 ± 0.7	0.391
mmol/mol	45 ± 7	45 ± 7	
HbA1c at 34 weeks	$N = 125$	$N = 54$	
%	6.4 ± 0.6	6.3 ± 0.7	0.276
mmol/mol	46 ± 6	45 ± 7	
% time spent below range (<3.5 mmol/L)			
Baseline ($N = -214$)	**8.0 ± 6.6 $N = 150$**	**10.4 ± 7.7** $N = 64$	**0.034**
24 weeks GA ($N = 180$)	5.0 ± 5.1 $N = 129$	5.6 ± 5.6 $N = 51$	0.716
34 weeks GA ($N = 154$)	4.9 ± 5.0 $N = 113$	5.6 ± 5.2 $N = 41$	0.411
Glycaemic Variability			
Glucose SD (mmol/l)			
Baseline ($N = -214$)	**3.01 ± 0.76 $N = 150$**	**3.32 ± 0.85 $N = 64$**	**0.044**
24 weeks GA ($N = 180$)	2.75 ± 0.65 $N = 129$	2.86 ± 0.74 $N = 51$	0.410
34 weeks GA ($N = 154$)	2.28 ± 0.58 $N = 113$	2.45 ± 0.78 $N = 41$	0.213
Glucose CV			
Baseline ($N = 214$)	**0.41 ± 0.08 $N = 150$**	**0.44 ± 0.08 $N = 64$**	**0.015**
24 weeks GA ($N = 180$)	0.36 ± 0.06 $N = 129$	0.37 ± 0.07 $N = 51$	0.459
34 weeks GA($N = 154$)	0.33 ± 0.06 $N = 113$	0.35 ± 0.08 $N = 41$	0.265

Note: Results shown are mean ± SD or *n* (%). Continuous variables were compared between groups using a *t*-test and categorical variables were compared with a Fisher's exact test. Bold indicate statistically significant values.

Abbreviations: CV, Coefficient of Variation; GA, gestational age; SD, standard deviation.

[a]Adjusted rate ratio 7.5 (95% CI: 4.6–12.7; $p < 0.001$), in Poisson regression model with treatment group, prenatal care and pre-pregnancy weight as covariates).

relationship at 24 (not shown) or 34 weeks GA. Time in the target range had a weak negative correlation with the HFS-II score at baseline and 34 weeks. There were also weak positive associations between the HFS-II score and both measures of glycaemic variability at baseline and week 34 (Figure S2). At 12 weeks there is a strong association between fear and HbA1c but at 34 weeks there is no longer an association (Figure S3).

4 | DISCUSSION

In this study, we found that 30% of our pregnant women with type 1 diabetes had impaired awareness of hypoglycaemia. Impaired awareness of hypoglycaemia was associated with more episodes of severe hypoglycaemia in the year prior to pregnancy and during pregnancy. Impaired awareness of hypoglycaemia was associated with more

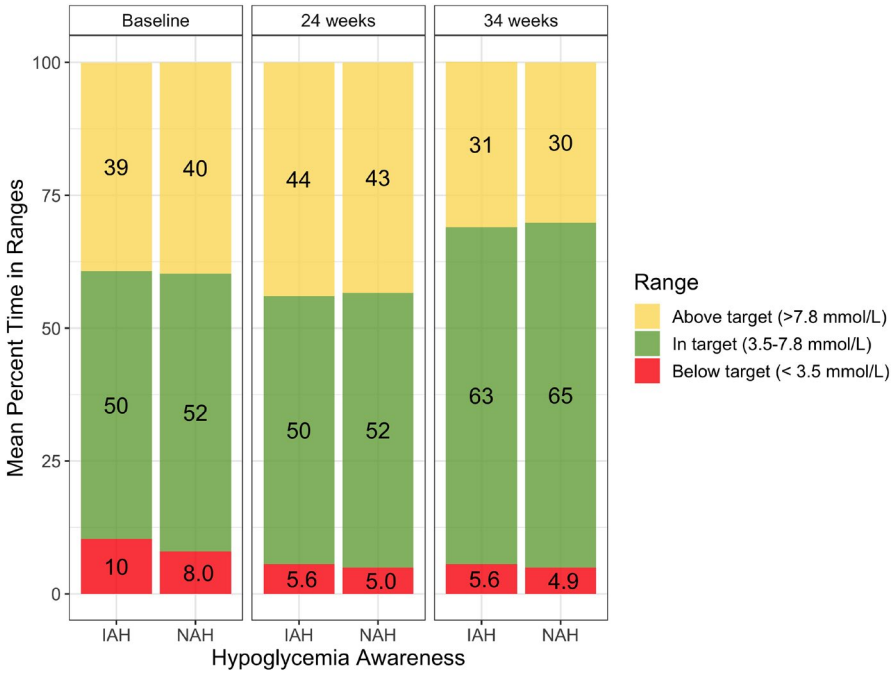

FIGURE 1 Per cent of time spent in the target range, above the target range and below the target range by hypoglycaemia awareness. IAH, impaired awareness of hypoglycaemia; NAH, normal awareness of hypoglycaemia. Per cent time below target at baseline (12 weeks) was higher in the impaired awareness of hypoglycaemia group compared to the NAH group, $p = 0.034$

time spent below the glycaemic target range and more glycaemic variability in the first trimester. Women with impaired awareness of hypoglycaemia had more fear of hypoglycaemia as measured by the HFS-II, and more worry about hypoglycaemia. Scoring high on the HFS-II was associated with a higher rate of maternal severe hypoglycaemia and a higher incidence of diabetic nephropathy. Women with impaired awareness of hypoglycaemia had less gestational weight gain. Reassuringly, there were no differences in neonatal outcomes in women with impaired awareness of hypoglycaemia compared to women with normal hypoglycaemia awareness. Scoring high on the HFS-II was associated with a lower incidence of neonatal hypoglycaemia.

We found that 30% of our pregnant women reported impaired awareness of hypoglycaemia. This is consistent with the only other study, Perea et al., which examined impaired awareness of hypoglycaemia in pregnant women with type 1 diabetes. This cohort study of 77 pregnant women found 24 (31.2%) of women reported impaired awareness of hypoglycaemia.[11] This is slightly higher than the 19.5%–25% rate of impaired awareness of hypoglycaemia found outside of pregnancy. Pregnant women may have higher rates of impaired awareness of hypoglycaemia due to the tighter glycaemic control and reduced counter-regulation seen during pregnancy.[14,15]

Our results show that women with impaired awareness of hypoglycaemia have more episodes of severe hypoglycaemia in the year prior to the pregnancy and more episodes during pregnancy. We also found that women with impaired awareness of hypoglycaemia spend more time below the target range and exhibit more glycaemic variability in the first trimester, all of which may contribute to and culminate in the increased episodes of severe hypoglycaemia seen. These findings are consistent with findings seen outside of pregnancy. Studies in non-pregnant patients have shown that impaired awareness of hypoglycaemia is associated with a 4–6-fold higher risk of severe hypoglycaemia.[21] Impaired awareness of hypoglycaemia has also been associated with a greater degree of glycaemic variability.[21] In a study of women with type 1 diabetes preconception, preconception counselling was shown to improve glycaemic variability but this did not improve awareness of hypoglycaemia.[22] Outside of pregnancy, the use of CGM has shown to be of benefit with a reduction in episodes of hypoglycaemic events in participants with impaired awareness of hypoglycaemia or severe hypoglycaemia[23] as well as a reduction of fear of hypoglycaemia and hypoglycaemia-related distress.[24] Our study did not show a reduction in severe hypoglycaemic events in those that used CGM as most hypoglycaemic events occurred prior to enrolment in the CONCEPTT study. Given the small number of severe hypoglycaemia events post-randomisation, we likely did not have the power to show a difference with the use of CGM. The use of CGM also did not demonstrate a reduction in time spent hypoglycaemic, although impaired awareness of hypoglycaemia was not associated with an increase in time spent hypoglycaemic in the second and third trimesters.

Consistent with clinical observations, our study has shown that pregnant women with impaired awareness of hypoglycaemia have more fear of hypoglycaemia. As well, fear of hypoglycaemia was associated with increased odds of having episodes of severe hypoglycaemia. In

TABLE 3 Maternal and neonatal outcomes by hypoglycaemia awareness

	Normal hypoglycaemia awareness ***N* = 150**	**Impaired awareness of hypoglycaemia** ***N* = 64**	***p* value**
Maternal Outcomes			
Worsening chronic HTN	4 (2.7)	2 (3.1)	1.000
Pre-eclampsia	16 (11)	11 (17)	0.260
Gestational HTN	13 (8.7)	4 (6.2)	0.783
Maternal Weight gain in kg			
Entry to 34 weeks	**14.2 ± 5.9** *N* = 130	**12.4 ± 4.9** *N* = 55	**0.043**
From 16 to 34 weeks	**10.1 ± 3.8** *N* = 128	**8.8 ± 3.5** *N* = 55	**0.031**
Birth Status	*N* = 147	*N* = 64	
Alive	141 (96)	59 (92)	0.351
Loss 20 weeks	5 (3.4)	4 (6.2)	
Stillborn	1 (0.7)	0 (0)	
Termination	0 (0.0)	1 (1.6)	
Neonatal Outcomes			
All reported as (*n* (%))	*N* = 141	*N* = 59	
Congenital Anomaly	2 (1.3)	3 (4.7)	0.159
Overall Preterm birth <37 weeks GA[a]	58 (41)	23 (38)	0.860
Early preterm <34 weeks GA[a]	13 (9.2)	3 (5)	0.475
GA at delivery	36.9 ± 1.8	37.0 ± 2.4	0.797
SGA <10th centile	4 (2.8)	0 (0)	0.451
LGA >90th centile	90 (64)	32 (54)	0.267
Birth injury	0 (0%)	1 (1.6)	0.299
Shoulder dystocia	0 (0%)	1 (1.6)	0.299
Neonatal hypoglycaemia	34 (23)	9 (14)	0.193
Hyperbilirubinemia	38 (25)	18 (28)	0.735
Respiratory distress syndrome	15 (10.0)	3 (4.7)	0.284
High-level neonatal care (NICU)	55 (37)	15 (23)	0.084
Infant length of hospital stay in days	6.0 ± 6.6	5.2 ± 6.2	0.416

Note: Results shown are mean ± SD or *n* (%). Bold indicate statistically significant values.

Abbreviations: GA, gestational age; HTN, hypertension; NICU, neonatal intensive care unit; SD, standard deviation.

[a]Amongst live births.

non-pregnant adults with impaired awareness of hypoglycaemia, recurrent severe hypoglycaemia was associated with fear of hypoglycaemia. Predictors of fear of hypoglycaemia include previous hypoglycaemia, increased age, female gender and higher education.[25] Fear of hypoglycaemia is also associated with poor sleep and anxiety/depression.[26] In our pregnant women, impaired awareness of hypoglycaemia or fear of hypoglycaemia should alert caregivers to their increased risk of severe hypoglycaemia during pregnancy.

As in our study, Perea et al. found that women with impaired awareness of hypoglycaemia had an increased rate of severe hypoglycaemia prior to pregnancy.[11] Unlike our study, they did not find an increase in severe hypoglycaemia during pregnancy in women with impaired awareness of hypoglycaemia, perhaps because of the smaller sample size. This study also found there were no differences in maternal or neonatal outcomes between women with impaired awareness of hypoglycaemia vs normal hypoglycaemia awareness although, unlike our study, they did find that infants of women with impaired awareness of hypoglycaemia had an increase in respiratory distress syndrome. They hypothesised that inflammation associated with hypoglycaemia may impair fetal lung development, as seen in animal models. Further research is needed to verify this outcome. In another study by Ringholm

TABLE 4 Hypoglycaemia Fear Survey II (HFS-II) scores at the baseline visit [a] by awareness

	Normal hypoglycaemia awareness $N = 142$	Impaired awareness of hypoglycaemia $N = 60$	*p* value
HFS-II Behaviour – avoidance subscale	8.1 ± 5.7	10.0 ± 7.0	0.120
HFS-II Behaviour – maintain high blood glucose subscale	3.9 ± 2.8	3.7 ± 2.7	0.672
HFS-II Worry subscale	**20.2 ± 14.4**	**25.9 ± 14.5**	**0.004**
HFS-II Total	**36.0 ± 20.4**	**43.7 ± 20.9**	**0.008**

Note: Results shown are mean ± SD, SD, standard deviation. Bold indicate statistically significant values.

[a]The Hypoglycaemia Fear Survey II includes 3 subscales, the Behaviour avoidance subscale which measure behaviors aimed to avoid hypoglycaemia or its consequences, the Behaviour maintain high blood glucose subscale, and the Worry subscale which measures concerns people may have around having episodes of hypoglycaemia. Higher scores indicate more fear of hypoglycaemia.

TABLE 5 Maternal and neonatal outcomes by Hypoglycemia Fear Survey II (HFS-II) scores. Odds ratios and the rate ratio are shown per 20 HFS-II points for each outcome, which is one between-person standard deviation of the HFS-II score

Maternal outcomes			
	Rate Ratio	95% confidence interval	*p* value
Maternal episodes of severe hypoglycemia[a]	**1.78**	**1.39, 2.27**	**<0.001**
	Odds Ratio	95% confidence interval	*p* value
Diabetes Complications			
Retinopathy[a]	1.33	0.97, 1.85	0.078
Nephropathy[b]	**1.92**	**1.07, 3.42**	**0.025**
Neuropathy[b]	0.94	0.41, 1.85	0.868
Worsening chronic HTN[b]	1.30	0.79, 2.07	0.279
Pre-eclampsia[a]	0.90	0.58, 1.37	0.637
Gestational HTN[b]	1.05	0.61, 1.68	0.858
Neonatal outcomes			
SGA <10th centile[b]	0.75	0.21,1.92	0.596
LGA >90th centile[a]	1.16	0.86, 1.57	0.321
Birth injury[b]	0.18	0.01, 2.29	0.327
Shoulder dystocia[b]	1.40	0.15, 9.17	0.726
Neonatal hypoglycemia[a]	**0.68**	**0.45, 1.00**	**0.050**
Hyperbilirubinemia[a]	1.12	0.81, 1.52	0.489
Respiratory distress syndrome[b]	1.26	0.79, 1.94	0.302
High level neonatal care (NICU)[a]	0.92	0.66, 1.24	0.591

Abbreviations: Bold indicate statistically significant values.

HTN, hypertension, LGA, large for gestational age, NICU, neonatal intensive care unit.

[a]The rate ratio and odds ratio are adjusted for maternal weight at study entry, randomised group from CONCEPTT, and a single variable representing use of either prenatal folic acid or prenatal vitamins.

[b]Unadjusted odds ratio.

Nielsen et al, hypoglycaemia awareness was prospectively evaluated from 8 to 33 weeks gestation in 108 women with type 1 diabetes.[27] They found that impaired hypoglycaemic awareness and previous severe hypoglycaemia were independent predictors of severe hypoglycaemic events during pregnancy, and if one had both risk factors, women were three times as likely to have a severe hypoglycaemic event. Most events occurred prior to 20 weeks gestation. Whilst birthweight was not different between the women with and without severe hypoglycaemia during pregnancy, this study did not compare maternal or neonatal outcomes in those with and without impaired hypoglycaemic awareness.

In our study, impaired awareness of hypoglycaemia was associated with reduced maternal weight gain up to 34 weeks GA. We postulate that women with impaired

awareness of hypoglycaemia may miss mild episodes of hypoglycaemia and, therefore, not treat them. The reduced caloric intake may then account for this difference in gestational weight gain. Of note, participants with impaired awareness of hypoglycaemia also had a higher BMI at baseline that may also have contributed to the reduced overall gestational weight gain compared to women with normal hypoglycaemia awareness.

An unexpected finding of our study was that increased fear of hypoglycaemia was associated with reduced neonatal hypoglycaemia. We would have expected patients with more fear of hypoglycaemia to have higher glycaemic excursions or overall glycaemic control above target, leading to more neonatal hypoglycaemia but we have in fact found the opposite. The reason for this is unknown. Our study is also the first to show increased diabetic nephropathy in pregnant women with fear of hypoglycaemia. Whilst the increased proteinuria was seen could also be due to other factors, such as preeclampsia, we did not see an increased incidence of preeclampsia or other hypertensive disorders of pregnancy between women with impaired awareness of hypoglycaemia vs normal hypoglycaemia awareness. Outside of pregnancy, impaired awareness of hypoglycaemia has been associated with more vascular complications in patients with type 2 diabetes.[28] There is also evidence for a relationship between severe hypoglycaemia and diabetes complications outside of pregnancy. The incidence of severe hypoglycaemia is higher in patients with type 2 diabetes who have macroalbuminuria.[29] The presence of diabetes complications (e.g. neuropathy) has also been shown to be independently related to the incidence of severe hypoglycaemia in patients with type 1 diabetes.[30]

What are the implications of this study? Having impaired awareness of hypoglycaemia and/or fear of hypoglycaemia as well as a history of severe hypoglycaemia should alert clinicians to their increased risk of severe hypoglycaemia. Although we did not show a reduced incidence of severe hypoglycaemia with CGM use, CGM was only started at 12 weeks. In a recent trial, the use of RT-CGM (with its alerts for impending and actual hypoglycaemia) was compared to intermittently scanned CGM (without alerts) in non-pregnant patients. They found that RT-CGM was associated with a reduction in severe hypoglycaemia and reduced fear of hypoglycaemia.[31] RT-CGM with alerts could be considered in these women with hypoglycaemia unawareness. There is evidence that insulin requirements go down between 7 and 12 weeks gestation.[32] Although studies have not shown an association between this reduction in dose and episodes of severe hypoglycaemia (Nielsen), increased vigilance may be necessary during this period.

Our study has several strengths. To our knowledge, this is the first study of impaired awareness of hypoglycaemia in pregnancy to have detailed and objective data about glycaemic outcomes derived prospectively from CGM data. The data are derived from a large, multicentre, well-characterised group of participants CONCEPTT was conducted across 31 sites and 5 countries, thus making our data generalizable. We also used a well-known and validated tool to assess fear of hypoglycaemia (HFS-II). The baseline characteristics of our study participants with normal hypoglycaemia awareness and impaired awareness of hypoglycaemia were similar, with the exception of prenatal vitamin and folic acid use. However, adjusting for these variables did not alter our results. We also acknowledge some limitations. First, we combined women who scored 'Sometimes Aware' and 'Never Aware' together, given the smaller sample size. Second, though fear of hypoglycaemia was measured by a validated tool, hypoglycaemia awareness was assessed by a single question. A validated questionnaire such as Clarke's hypoglycaemia awareness survey would provide more robust data about impaired awareness of hypoglycaemia status.[33] Despite this, episodes of severe hypoglycaemia and fear of hypoglycaemia were associated with our definition of impaired awareness of hypoglycaemia, making it clinically plausible. This is a pre-planned sub-study with several outcomes examined, and as with any observational study, there is potential for confounding of impaired awareness with other characteristics that may be related to outcomes. Given that this was not our primary question in the original trial, we may not have the power to detect small, clinically important differences. Finally, CGM data were only available for 1 week at 12, 24 and 34 weeks. Most often hypoglycaemia occurs in the first and early second trimester of pregnancy[7] and we only enrolled women at the end of the first trimester; thus, potentially missing hypoglycaemia. Therefore, the results we obtained at 12 weeks may have been even more striking earlier in the first trimester. We did, however, ask systematically about episodes of severe hypoglycaemia that occurred during early pregnancy, prior to enrolment.

In summary, impaired awareness of hypoglycaemia and/or fear of hypoglycaemia was associated with increased severe hypoglycaemia during pregnancy. Having impaired awareness of hypoglycaemia or fear of hypoglycaemia should alert clinicians to this increased risk of severe hypoglycaemia. Women with impaired awareness of hypoglycaemia have less maternal weight gain and reassuringly, no adverse neonatal outcomes. Our study is one of the first to include patient-reported measures with objective CGM measures and with severe hypoglycaemia and other maternal and neonatal outcomes collected prospectively. Future studies should focus on understanding the mechanism of impaired awareness of hypoglycaemia and fear of hypoglycaemia in pregnancy and determine whether there are longer-term consequences on mothers and babies.

ACKNOWLEDGEMENTS

We thank all the women in the CONCEPTT trial for their participation in the trial and acknowledge the invaluable support from the collaborating clinical care teams and the Clinical Trials Services/Centre for Mother, Infant and Child Research team at Sunnybrook Research Institute, Toronto, Canada, in particular Sonya Mergler, Kathryn Mangoff and Gail Klein.

CONFLICT OF INTEREST

DSF and HRM report grants from the Juvenile Diabetes Research Foundation during the conduct of the CONCEPTT study. DSF sits on the EXPECT Advisory Panel and reports personal fees from Novo Nordisk outside the submitted work. HRM reports personal fees from Novo Nordisk, Roche, and Medtronic, outside the submitted work. HRM sits on the Medtronic European Scientific Advisory Board. All remaining authors declare no competing interests.

ORCID

Helen R. Murphy https://orcid.org/0000-0001-6876-8727
Denice S. Feig https://orcid.org/0000-0001-8561-7584

REFERENCES

1. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet*. 2017;390:2347-2359.
2. Feig DS, Hwee J, Shah BR, et al. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. *Diabetes Care*. 2014;37:1590-1596.
3. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. *Diabetes Care*. 2009;32:2005-2009.
4. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, et al. Hypoglycaemia in pregnant women with type 1 diabetes: predictors and role of metabolic control. *Diabetes Care*. 2008;31:9-14.
5. Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. *Diabetes Care*. 2010;33:2514-2520.
6. Leinonen PJ, Hiilesmaa VK, Kaaja RJ, et al. Maternal mortality in type 1 diabetes. *Diabetes Care*. 2001;24:1501-1502.
7. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, et al. Hypoglycaemia during pregnancy in women with Type 1 diabetes. *Diabet Med*. 2012;29:558-566.
8. Ringholm L, Secher AL, Pedersen-Bjergaard U, et al. The incidence of severe hypoglycaemia in pregnant women with type 1 diabetes mellitus can be reduced with unchanged HbA1c levels and pregnancy outcomes in a routine care setting. *Diabetes Res Clin Pract*. 2013;101:123-130.
9. Diabetes Canada Clinical Practice Guidelines Expert Committee, Yale JF, Paty B, et al. Hypoglycaemia. *Can J Diabetes* 2018;42(Suppl 1):S104-S108.
10. Rosenn BM, Miodovnik M, Holcberg G, et al. Hypoglycaemia: the price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. *Obstet Gynecol*. 1995;85:417-422.
11. Perea V, Bertran B, Bellart J, et al. Impaired awareness of hypoglycaemia: a new risk factor for adverse pregnancy outcomes in type 1 diabetes. *Diabetes Metab Res Rev*. 2019;35:e3176.
12. Evers IM, ter Braak EW, de Valk HW, et al. Risk indicators predictive for severe hypoglycaemia during the first trimester of type 1 diabetic pregnancy. *Diabetes Care*. 2002;25:554-559.
13. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycaemia in patients with type I diabetes with impaired awareness of hypoglycaemia. *Diabetes Care*. 1994;17:697-703.
14. Diamond MP, Reece EA, Caprio S, et al. Impairment of counterregulatory hormone responses to hypoglycaemia in pregnant women with insulin-dependent diabetes mellitus. *Am J Obstet Gynecol*. 1992;166:70-77.AA.
15. Rosenn BM, Miodovnik M, Khoury JC, et al. Counterregulatory hormonal responses to hypoglycaemia during pregnancy. *Obstet Gynecol*. 1996;87:568-574.
16. Henriksen MM, Andersen HU, Thorsteinsson B, et al. Hypoglycaemic exposure and risk of asymptomatic hypoglycaemia in type 1 diabetes assessed by continuous glucose monitoring. *J Clin Endocrinol Metab*. 2018;103:2329-2335.
17. Beck RW, Bergenstal RM, Riddlesworth TD, et al. The association of biochemical hypoglycaemia with the subsequent risk of a severe hypoglycaemic event: analysis of the DCCT data set. *Diabetes Technol Ther*. 2019;21:1-5.
18. Feig DS, Asztalos E, Corcoy R, et al. CONCEPTT: continuous glucose monitoring in women with type 1 diabetes in pregnancy trial: a multi-center, multi-national, randomized controlled trial - study protocol. *BMC Pregnancy Childbirth*. 2016;16:167.
19. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycaemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care*. 2011;34:801-806.
20. Gonder-Frederick LA, Vajda KA, Schmidt KM, et al. Examining the behaviour subscale of the hypoglycaemia fear survey: an international study. *Diabet Med*. 2013;30:603-609.
21. Lin YK, Hung M, Sharma A, et al. Iimpaired awareness of hypoglycaemia continues to be a risk factor for severe hypoglycaemia despite the use of continuous glucose monitoring system in type 1 diabetes. *Endo Practice*. 2019;25:517-525.37
22. Perea V, Giménez M, Amor AJ, et al. Prepregnancy care in women with type 1 diabetes improves HbA1c and glucose variability without worsening hypoglycaemia time and awareness: glycaemic variability during prepregnancy care. *Diabetes Res Clin Pract*. 2019;154:75-81.
23. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglcaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet*. 2018;391:1367-1377.
24. Ehrmann D, Heinemann L, Freckmann G, et al. The effects and effect sizes of real-time continuous glucose monitoring on patient-reported outcomes: a secondary analysis of the HypoDE study. *Diab Tech Ther*. 2019;21:86-93.
25. Chiara Rossi M, Nicolucci A. ,Ozzellow A et al. Impact of severe and symptomatic hyplycemia on quality of life and fear of hypoglycaemia in type 1 and type 2 diabetes. Results of

the Hypos-1 observational study. *Nutr Metab Cardiovasc Dis*. 2019;29:736-743.
26. Suteau V, Saulnier P-J, Wargny M, et al. Association between sleep disturbances, fear of hypoglycaemia and psychological well-being in adults with type 1 diabetes mellitus, data from cross-sectional VARDIA study. *Diab Res and Clin Pract*. 2020;160:107988.
27. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, et al. Hypoglycemia in pregnant women with type 1 diabetes. *Diabetes Care*. 2008;31:9-14.
28. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycaemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410-1418.
29. Yun JS, Ko SH, Ko SH, et al. Presence of macroalbuminuria predicts severe hypoglycaemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care*. 2013;36:1283-1289.
30. ter Braak EW, Appelman AM, van de Laak M, et al. Clinical characteristics of type 1 diabetic patients with and without severe hypoglycaemia. *Diabetes Care*. 2000;23:1467-1471.
31. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1):a 6-month, prospective, multicentre, randomised controlled trial. *Lancet*. 2021;397(10291):2275-2283.
32. Jovanovic L, Knopp RH, Brown Z, et al. Declining insulin requirement in the late first trimester of diabetic pregnancy. *Diabetes Care*. 2001;24:1130-1136.
33. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18:517-522.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Bahrami J, Tomlinson G, Murphy HR, Feig DS; the CONCEPTT Collaborative Group. Impaired awareness of hypoglycaemia in women with type 1 diabetes in pregnancy: Hypoglycaemia fear, glycaemic and pregnancy outcomes. *Diabet Med*. 2022;00:e14789. doi:10.1111/dme.14789