RESEARCH: COMPLICATIONS

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

Jasmine Bahrami1,2 | George Tomlinson1,3 | Helen R. Murphy4,5 | Denice S. Feig1,2,6 | the CONCEPTT Collaborative Group†

1Department of Medicine, University of Toronto, Toronto, Canada
2Leadership Sinai Centre for Diabetes, Mt Sinai Hospital, Sinai Health System, Toronto, Ontario, Canada
3University Health Network, Toronto, Ontario, Canada
4Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
5Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, UK
6Lunenfeld-Tanenbaum Research Institute, Toronto, Ontario, Canada

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.
INTRODUCTION

Pregnant women with type 1 diabetes are at increased risk of maternal and neonatal complications.\textsuperscript{1–3} Improving glycaemia before and during pregnancy reduces the risk of many complications, including congenital malformations, pre eclampsia and preterm delivery.\textsuperscript{4–6} However, striving for tight pregnancy glucose targets is associated with an increased frequency of hypoglycaemic episodes, including severe hypoglycaemia.\textsuperscript{7,8} Severe hypoglycaemia is defined as any hypoglycaemic episode requiring the assistance of a third party.\textsuperscript{9} Most severe hypoglycaemia episodes occur in early pregnancy, with the highest incidence between 8 and 16 weeks of gestation.\textsuperscript{4,10} Severe hypoglycaemia is associated with an increased risk of seizures, hospitalizations and maternal death.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{14,15} Furthermore, frequent episodes of hypoglycaemia, often seen during pregnancy, also predispose to impaired awareness of hypoglycaemia, which in turn leads to an increased risk of severe hypoglycaemia.\textsuperscript{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,
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. 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 (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. 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. 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 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,
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
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).

### TABLE 2 Glycaemic outcomes of pregnant participants in CONCEPTTT 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       | 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)    | 0.35 ± 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.

*aAdjusted 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.

### 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
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. 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 hypoglycaemia23 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 CONCEPTTT 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
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.\textsuperscript{25} Fear of hypoglycaemia is also associated with poor sleep and anxiety/depression.\textsuperscript{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.\textsuperscript{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

\begin{table}
\centering
\caption{Maternal and neonatal outcomes by hypoglycaemia awareness}
\begin{tabular}{|l|l|l|l|}
\hline
 & \textbf{Normal hypoglycaemia awareness} & \textbf{Impaired awareness of hypoglycaemia} & \textbf{p value} \\
 & \textit{N} = 150 & \textit{N} = 64 & \\
\hline
\textbf{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 \\
\hline
Maternal Weight gain in kg & & & \\
Entry to 34 weeks & 14.2 ± 5.9 & 12.4 ± 4.9 & \textbf{0.043} \\
& \textit{N} = 130 & \textit{N} = 55 & \\
From 16 to 34 weeks & 10.1 ± 3.8 & 8.8 ± 3.5 & \textbf{0.031} \\
& \textit{N} = 128 & \textit{N} = 55 & \\
\hline
\textbf{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) & \\
\hline
\textbf{Neonatal Outcomes} & & & \\
All reported as (n (%)) & \textit{N} = 141 & \textit{N} = 59 & \\
Congenital Anomaly & 2 (1.3) & 3 (4.7) & 0.159 \\
Overall Preterm birth <37 weeks GA\textsuperscript{a} & 58 (41) & 23 (38) & 0.860 \\
Early preterm <34 weeks GA\textsuperscript{a} & 13 (9.2) & 3 (5) & 0.475 \\
GA at delivery & 36.9 ± 1.8 & 37.0 ± 2.4 & 0.797 \\
SGA <10\textsuperscript{th} centile & 4 (2.8) & 0 (0) & 0.451 \\
LGA >90\textsuperscript{th} 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 \\
\hline
\end{tabular}
\footnote{Note: Results shown are mean ± SD or n (%). Bold indicate statistically significant values.}
\footnote{Abbreviations: GA, gestational age; HTN, hypertension; NICU, neonatal intensive care unit; SD, standard deviation.}
\footnote{\textsuperscript{a}Amongst live births.}
\end{table}
Nielsen et al, hypoglycaemia awareness was prospectively evaluated from 8 to 33 weeks gestation in 108 women with type 1 diabetes. 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 be less able to modify their lifestyle or treatment to cope with hypoglycaemia, leading to increased risk of severe events.

### Table 5: Maternal and neonatal outcomes by Hypoglycaemia 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**

| Diabetes Complications   | Rate Ratio | 95% confidence interval | p value |
|--------------------------|------------|-------------------------|---------|
| Maternal episodes of severe hypoglycaemia<sup>a</sup> | 1.78       | 1.39, 2.27              | <0.001  |
| Nonsialysis | 1.33 | 0.97, 1.85 | 0.078 |
| Nephropathy<sup>b</sup> | 1.92 | 1.07, 3.42 | 0.025 |
| Neuropathy<sup>b</sup> | 0.94 | 0.41, 1.85 | 0.868 |
| Worsening chronic HTN<sup>b</sup> | 1.30 | 0.79, 2.07 | 0.279 |
| Pre-eclampsia<sup>a</sup> | 0.90 | 0.58, 1.37 | 0.637 |
| Gestational HTN<sup>b</sup> | 1.05 | 0.61, 1.68 | 0.858 |

**Neonatal outcomes**

| SGA <10<sup>th</sup> centile<sup>b</sup> | 0.75 | 0.21, 1.92 | 0.596 |
| LGA >90<sup>th</sup> centile<sup>a</sup> | 1.16 | 0.86, 1.57 | 0.321 |
| Birth injury<sup>b</sup> | 0.18 | 0.01, 2.29 | 0.327 |
| Shoulder dystocia<sup>b</sup> | 1.40 | 0.15, 9.17 | 0.726 |
| Neonatal hypoglycaemia<sup>a</sup> | 0.68 | 0.45, 1.00 | 0.050 |
| Hyperbilirubinemia<sup>a</sup> | 1.12 | 0.81, 1.52 | 0.489 |
| Respiratory distress syndrome<sup>b</sup> | 1.26 | 0.79, 1.94 | 0.302 |
| High level neonatal care (NICU)<sup>a</sup> | 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.
- 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.
- Unadjusted odds ratio.
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. 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. 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.

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. 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. 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. 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 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.
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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
Denise S. Feig  https://orcid.org/0000-0001-8561-7584

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**SUPPORTING INFORMATION**

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

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