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Maternal glycaemic control and risk of neonatal hypoglycaemia in Type 1 diabetes pregnancy: a secondary analysis of the CONCEPTT trial

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What's new?

- Neonatal hypoglycaemia is a common complication of Type 1 diabetes pregnancy.
- This study found that 15% of term and 40% of preterm infants had neonatal hypoglycaemia requiring treatment with intravenous dextrose.

- Modest differences in continuous glucose monitoring time-in-target (5–7% increase) and HbA_{1c} [4 mmol/mol (0.4%) decrease] during the second and third trimesters are associated with lower risk of neonatal hypoglycaemia.
- Clinicians should focus on improving maternal glucose control thereby reducing fetal hyperinsulinemia during the second and third trimesters to reduce the risk of neonatal hypoglycaemia.

Abstract

Aims To examine the relationship between maternal glycaemic control and risk of neonatal hypoglycaemia using conventional and continuous glucose monitoring metrics in the Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial (CONCEPTT) participants.

Methods A secondary analysis of CONCEPTT involving 225 pregnant women and their liveborn infants. Antenatal glycaemia was assessed at 12, 24 and 34 weeks gestation. Intrapartum glycaemia was assessed by continuous glucose monitoring measures 24 hours prior to delivery. The primary outcome was neonatal hypoglycaemia defined as glucose concentration < 2.6 mmol/l and requiring intravenous dextrose.

Results Neonatal hypoglycaemia occurred in 57/225 (25.3%) infants, 21 (15%) term and 36 (40%) preterm neonates. During the second and third trimesters, mothers of infants with neonatal hypoglycaemia had higher HbA_{1c} [48 ± 7 (6.6 ± 0.6) vs. 45 ± 7 (6.2 ± 0.6); $P = 0.0009$ and 50 ± 7 (6.7 ± 0.6) vs. 46 ± 7 (6.3 ± 0.6); $P = 0.0001$] and lower continuous glucose monitoring time-in-range (46% vs. 53%; $P = 0.004$ and 60% vs. 66%; $P = 0.03$). Neonates with hypoglycaemia had higher cord blood C-peptide concentrations [1416 (834, 2757) vs. 662 (417, 1086) pmol/l; $P < 0.00001$], birthweight > 97.7th centile (63% vs. 34%; $P < 0.0001$) and skinfold thickness ($P \leq 0.02$). Intrapartum continuous glucose monitoring was available for 33 participants, with no differences between mothers of neonates with and without hypoglycaemia.

Conclusions Modest increments in continuous glucose monitoring time-in-target (5–7% increase) during the second and third trimesters are associated with reduced risk for neonatal hypoglycaemia. While more intrapartum continuous glucose monitoring data are needed, the higher birthweight and skinfold measures associated with neonatal hypoglycaemia suggest that risk is related to fetal hyperinsulinemia preceding the immediate intrapartum period.

<H1>Introduction

Neonatal hypoglycaemia is a common complication in pregnancies associated with maternal diabetes (1). In the short term, neonatal hypoglycaemia requires careful monitoring and may require treatment such as intravenous dextrose and/or admission to the neonatal intensive care unit, which incurs substantial healthcare costs. This leads to maternal and infant separation, with implications for breastfeeding initiation, and even transient hypoglycaemia has been associated with longer term neurodevelopmental impairment into childhood (2).

Type 1 diabetes is a well-established risk factor for neonatal hypoglycaemia (3). Theoretically, limiting maternal intrapartum hyperglycaemia reduces the risk of neonatal hypoglycaemia by preventing an acute rise in fetal insulin secretion before birth. The Joint British Diabetes Societies, National Institute for Health and Clinical Excellence and Canadian guidelines recommend tight intrapartum glucose targets (4.0–7.0 mmol/l) during labour and delivery (4-6). However, there are insufficient high quality data confirming an association between maternal intrapartum glucose control and neonatal hypoglycaemia. The potential for neonatal benefit must also be balanced against the demands on patients and healthcare teams and risk of maternal hypoglycaemia (1, 7-9).

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated continuous associations of maternal glucose levels at 24–32 weeks with neonatal hypoglycaemia (10). The HAPO

investigators also demonstrated that birthweight > 90th centile and higher percentage of body fat were associated with increased risk of neonatal hypoglycaemia. This study, among others, suggests that maternal hyperglycaemia throughout pregnancy may be of greater importance than short duration intrapartum glucose control (10, 11).

The Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial (CONCEPTT) was a multicentre trial that randomized women to real-time continuous glucose monitoring (CGM) or standard capillary glucose monitoring (12). It described significantly less neonatal hypoglycaemia in infants of women randomized to CGM compared with standard glucose monitoring, however, a detailed analysis of the relative importance of intrapartum and antenatal glucose was not performed.

No studies have examined the relationship between neonatal hypoglycaemia and both maternal antepartum and intrapartum glycaemic control using CGM. Our aim was to examine the relationship between maternal glycaemic control and risk of neonatal hypoglycaemia using conventional and CGM metrics in women with Type 1 diabetes. A secondary objective was to explore the associations between maternal glycaemia and birthweight percentile, neonatal anthropometry measures and fetal hyperinsulinemia assessed by cord blood C-peptide.

<H1>Participants and methods

<H2>Study design and population

This was a cohort study including all participants in CONCEPTT who had a live birth (n = 225). The details of CONCEPTT have been previously published (12). In brief, CONCEPTT was a multicentre randomized control trial of real-time CGM in pregnant women or women planning pregnancy. Eligible women with Type 1 diabetes who were either < 14 weeks pregnant (pregnancy trial) or

planning pregnancy (planning pregnancy trial) were randomized to CGM or capillary glucose monitoring. Women randomized to capillary glucose monitoring had masked CGM for 6 days at baseline, 24 and 34 weeks gestation. Intrapartum use of CGM was not part of the clinical study protocol, therefore glucose monitoring during labour and delivery was determined by participants and their local healthcare teams.

<H2>Definitions and outcomes measures

Antepartum glycaemic control was assessed using CGM in the first trimester (before 13 weeks and 6 days in the pregnancy trial and at 12 weeks gestation in the planning pregnancy trial), 24 and 34 weeks gestation as per the CONCEPTT protocol. The intrapartum period was defined as the 24 hours prior to delivery. This definition of intrapartum glycaemic control was based on published data (13, 14) and agreed prior to data analysis. Only participants with at least 12 hours of CGM data before delivery were included. Continuous glucose monitoring measures [mean glucose, time-in-target, time-above and below-target and glycaemic variability measures [SD, coefficient of variation (CV)] during the 24 hours were assessed. Target range both antepartum and intrapartum was defined as 3.5–7.8 mmol/l.

The primary outcome of interest was clinical neonatal hypoglycaemia, which was defined as having a documented glucose concentration of < 2.6 mmol/l and requiring treatment with IV dextrose within the first 48 hours. Neonatal hypoglycaemia was treated as per local practice across the 31 sites. Fetal hyperinsulinemia was assessed by cord blood C-peptide, with samples centrifuged immediately after birth, kept on ice and stored at -80°C within 2 hours following delivery. Plasma C-peptide concentration was measured within one run of a solid-phase, competitive chemiluminescent immunoassay (intraassay and interassay coefficient of variation of < 6%; DynaCare, Brampton, Ontario, Canada). For analysis, both the absolute C-peptide measurements as well as the categorical variable of > or ≤ 90th centile in the HAPO study were used (10). Fetal anthropometric measures

(triceps, subscapular, biceps and suprailiac skinfolds) were performed using calibrated equipment within 72 hours of birth by trained research staff. Large for gestational age was defined as > 90th centile and extreme large for gestational age was defined as > 97.7th centile using gestation related optimal weight (GROW) software (15).

<H2>Statistical analysis

Continuous data were compared using t-tests or by the Mann-Whitney test and categorical data were compared using chi-square tests. Univariate logistic regression was used to screen for potential associations between neonatal hypoglycaemia and variables identified as clinically important. Multiple logistic regression was carried out using variables identified in these univariate analyses. In cases where variables were highly correlated (e.g., most measures of maternal glycaemia), the variable with the strongest association (defined by the highest standardized OR) and/or those available at time of delivery was included in the final model. We performed a prespecified assessment for effect modification by preterm delivery using a likelihood-ratio test, and a stratified analysis was performed when modification was identified. Additionally, we assessed for potential confounding by smoking, diabetes duration and education level. Given the limited number of neonates with hypoglycaemia, we aimed to include a variable only if it was identified as a confounder, that is, if its addition to a regression model with large for gestational age and HbA_{1c} changed the odds ratio (OR) for HbA_{1c} by > 10%. Adjusted ORs are presented only if confounding was identified. Results are presented as OR [95% confidence intervals (CI)]. All analyses were performed using STATA version 14.1 (Stata Corp., College Station, TX, USA). A two-sided *P*-value of < 0.05 was considered statistically significant.

<H1>Results

Two hundred and twenty-five CONCEPTT participants had live births and were included in this cohort, of whom 200 participated in the pregnancy trial and 25 in the planning pregnancy trial.

Neonatal hypoglycaemia occurred in 57 (25%) of infants (43 and 14 infants in the pregnancy and planning pregnancy trial, respectively). Maternal and neonatal characteristics of those with and without neonatal hypoglycaemia are shown in Table 1. Mothers of neonates with neonatal hypoglycaemia were more likely to use insulin pump therapy. Neonates with hypoglycaemia were more likely to be delivered by caesarean section, preterm and admitted to the neonatal intensive care unit and less likely to be exclusively breastfed at discharge. They had higher customized birthweight percentile, and higher rates of large and extreme large for gestational age.

<H2>Antepartum glycaemic control

There were no differences in HbA_{1c} or any CGM measures during the first trimester. However, in both the second and third trimesters, mothers of infants with neonatal hypoglycaemia had suboptimal glucose control with higher HbA_{1c} levels, less time spent in the target glucose range, and more time-above-target both at 24 and at 34 weeks gestation.

<H2>Intrapartum glycaemic control

Intrapartum CGM data were available for only 33 of the 225 women included (n = 29 real-time CGM and n = 4 masked CGM). There were no differences in neonatal hypoglycaemia, preterm delivery, birthweight centile, HbA_{1c} or pump use in women who continued CGM intrapartum compared with those who did not (data not presented). However, mothers who used intrapartum CGM were older (33.4 vs. 31.2 years; P = 0.009) and more likely to be randomized to CGM than to capillary glucose monitoring (88 vs. 12%; P < 0.0001).

There were no significant differences in any CGM measures during the 24 hours prior to delivery between mothers of neonates with and without hypoglycaemia (Table 2). Specifically, mothers of infants with neonatal hypoglycaemia had comparable mean glucose and last glucose prior to delivery. Mothers of infants with neonatal hypoglycaemia spent 76% time in target in the 24 hours prior to delivery, which while numerically lower than mothers without neonatal hypoglycaemia (82%), was not statistically different ($P = 0.82$). There was minimal hypoglycaemia in both groups and no difference in glucose variability (SD and CV) measures.

<INSERT TABLE 2>

<H2>Neonatal hypoglycaemia, adiposity and hyperinsulinemia

Skinfold measurements were available in 150 infants and cord blood C-peptide levels were available in 143 cases. Neonates with hypoglycaemia had significantly higher adiposity by skinfold thickness measurements (Table 3). Neonates with hypoglycaemia also had evidence of hyperinsulinemia with significantly higher cord blood C-peptide levels [median (IQR) 1416 (834, 2757) vs. 662 (417, 1086); $P < 0.00001$). They also had a significantly higher proportion with cord blood C-peptides > 90th centile (10).

Cord blood C-peptide was higher in preterm neonates, large and extreme large for gestational age neonates and, if antenatal steroids were given as well, as in neonates born in the UK, Canada, Ireland or the USA compared with those born in Spain or Italy (Table S1).

Cord blood C-peptide was lower in participants who achieved in-target glycaemic control in the second and third trimesters, defined as $HbA_{1c} < 6.5\%$, compared with those that did not (Table S1).

Post-hoc analyses revealed no difference in cord C-peptide levels of women who were overweight compared with women with normal weight in early pregnancy. There was also no difference in cord C-peptide levels in women with excessive compared with appropriate gestational weight gain defined by the Institute of Medicine guidelines (16). Neonates with cord blood C-peptide > 90th centile by HAPO criteria had significantly higher adiposity as assessed by skinfold thickness than those ≤ 90th centile by HAPO criteria [sum of four skinfolds (triceps, subscapular, biceps and flank) 24.5 ± 5.7 vs. 19.2 ± 3.8 mm, respectively; $P < 0.00001$].

<H2>Logistic regression analysis

Univariate logistic regression identified gestational age at delivery, large and extreme large for gestational age, antenatal glycaemia (second and third trimester HbA_{1c} and CGM measures), insulin pump use, caesarean delivery and cord blood C-peptide concentration as being significantly associated with neonatal hypoglycaemia (Table S2).

In all neonates, extreme large for gestational age [OR 2.5 (95% CI 1.3, 5.0); $P = 0.007$) and third trimester HbA_{1c} [OR 2.3 (95% CI 1.4, 4.0); $P = 0.002$] were significantly associated with increased odds of neonatal hypoglycaemia (Table 4). However, in the prespecified analysis, preterm delivery was a significant effect modifier in the relationship between extreme large for gestational age and neonatal hypoglycaemia in the overall model (*P*-value for interaction term 0.02) so a stratified analysis was performed. In term neonates, extreme large for gestational age [OR 6.2 (95% CI 1.8, 21.0); $P = 0.003$] and third trimester HbA_{1c} [OR 3.5 (95% CI 1.4, 9.0); $P = 0.01$] were significantly associated with increased odds of neonatal hypoglycaemia (Table 4). However, in preterm neonates, neither extreme large for gestational age [OR 1.3 (95% CI 0.5, 3.2); $P = 0.57$] nor third trimester HbA_{1c} [OR 1.2 (95% CI 0.6, 2.5); $P = 0.58$] were significantly associated with increased odds of neonatal hypoglycaemia, although the CIs are too wide to rule out a positive or negative association in this group. Smoking, diabetes duration and education level were all assessed as potential confounders.

Since adjustment for these variables did not change the OR by > 10% and our small sample size and number of events were small in the subgroups, we presented the unadjusted models only.

<INSERT TABLE 4>

<H1>Discussion

Maternal antenatal glucose control, as measured by HbA_{1c} and CGM during the second and third trimesters, is associated with clinically relevant neonatal hypoglycaemia. Taken together with the CONCEPTT trial results, our data suggest that modest improvements in maternal glycaemia, in the order of a 4 mmol/mol (0.4%) decrease in HbA_{1c} or a 5–7% increased CGM time-in-target range, is associated with reductions in neonatal hypoglycaemia. We did not find differences in intrapartum glycaemic control, although statistical power was limited by the small numbers of women who continued using CGM until delivery.

The mechanism of neonatal hypoglycaemia appears to be fetal hyperinsulinemia as demonstrated by the high concentration of cord blood C-peptide, markers of infant size (birthweight centile) and infant adiposity (skinfold measurements) in neonates with hypoglycaemia. Interestingly, participants from Mediterranean countries (Spain and Italy) had significantly lower C-peptide concentrations. We hypothesize that this reflects the lower rates of large for gestational age in Spain and Italy, as well as a combination of glycaemic control, genetic, dietary and environmental factors (12). The HAPO investigators previously demonstrated that the odds of neonatal hypoglycaemia increased in a graded way with increasing cord blood C-peptide levels (10). They also noted birthweight > 90th centile and higher percentage of body fat were associated with higher C-peptide levels. Our study demonstrated that achieving target HbA_{1c} at 24 and 34 weeks gestation is associated with lower C-peptide levels in Type 1 diabetes pregnancies, suggesting that it is more than just the immediate intrapartum period that contributes to fetal hyperinsulinemia.

Like previous studies, our analysis highlights the association between antenatal glycaemic control and increased risk of neonatal hypoglycaemia (11, 17). However, our study includes detailed CGM measures during pregnancy, suggesting that interventions to improve second and third trimester glucose control may be more impactful for reducing the risk of neonatal hypoglycaemia than intrapartum interventions. In the pregnancy trial in CONCEPTT, CGM led to a 50% reduction in the OR for neonatal hypoglycaemia (15 vs. 28%; $P = 0.03$). In this secondary analysis, both women with and without neonatal hypoglycaemia spent more time in target range in the intrapartum period (76.0 and 81.8%, respectively) compared with 34 weeks gestation (60.1 and 65.7%, respectively). This is consistent with the closed-loop studies in pregnancy that demonstrate a higher time in target in the intrapartum period compared with earlier in pregnancy (13, 18, 19). While insulin pump use during pregnancy was associated with increased risk of neonatal hypoglycaemia, there was no increased risk associated with continuing pump therapy during labour and delivery, consistent with recent data (20). Given the limited hyperglycaemia in the intrapartum period, it seems unlikely that closed-loop insulin delivery would reduce intrapartum hyperglycaemia, although it may be useful for limiting maternal hypoglycaemia, more resource-efficient than intravenous insulin regimens, and preferable for women to manage their own diabetes (13).

We also found extreme large for gestational age was associated with 6-fold increased odds of neonatal hypoglycaemia in term neonates. This increased risk of neonatal hypoglycaemia observed with larger neonates is also consistent with previous literature (21-23). It is important that clinicians are aware of the compounding effect of infant size when managing term babies on the post-natal ward. Interestingly, we found that preterm birth was a significant effect modifier in the relationship between extreme large for gestational age and neonatal hypoglycaemia. We postulate that preterm delivery alone is associated with such a high risk of neonatal hypoglycaemia, and that additional risk factors do not play as large a role. Future research should consider whether routine administration of buccal mucosa dextrose could reduce the risk of neonatal hypoglycaemia in high-risk preterm Type 1 diabetes offspring (24).

The literature supporting the importance of intrapartum control is inconsistent (1). Only a few studies have used CGM to characterize intrapartum glycaemic control (13, 14, 22, 25). A pilot study evaluating closed-loop during labour and delivery (n = 27 participants) found comparable intrapartum glycaemia (82% time in target range) with CONCEPTT participants without neonatal hypoglycaemia, also with no between-group differences according to the presence or absence of neonatal hypoglycaemia (13). Another study (n = 16 participants) examining the feasibility of paired maternal intrapartum CGM and newborn CGM found a lower but not statistically significant intrapartum CGM time-in-target in mothers of neonates requiring intravenous glucose (65 vs. 90%; P = 0.16) (14). Cordua *et al*. found that time spent > 7.0 mmol/l was higher in mothers of neonates with hypoglycaemia, but their study lacked details of antepartum glycaemia as measured by CGM (22). Stenninger *et al*. reported a higher mean glucose concentration 2 hours before delivery in 15 women with Type 1, Type 2 and gestational diabetes (25). It is implausible that the markers of fetal hyperinsulinemia and neonatal adiposity in our study could have been attributed to 2 hours of suboptimal glycaemia. Large, high quality, randomized controlled trials of strict vs. more relaxed intrapartum targets would be needed to determine if the benefits of strict glycaemic control during this period outweigh the risks in women with Type 1 diabetes.

Our study has several strengths. It is a large, multicentre, well-characterized cohort of women with Type 1 diabetes with detailed information regarding glycaemic control as assessed by both HbA_{1c} and CGM. The data were prospectively collected and rigorously evaluated with standardized central laboratory HbA_{1c} and C-peptide measurements and a robust, clinically meaningful definition of neonatal hypoglycaemia. This is the largest contemporary cohort of women with Type 1 diabetes in whom cord blood C-peptide and detailed neonatal anthropometry measures are available.

We also acknowledge its limitations, most notably the small number of women who used CGM during labour and delivery. Given our sample size, we cannot exclude that intrapartum glycaemic control may be associated with neonatal hypoglycaemia. We estimate that to detect a clinically relevant 5% increase, CGM time-in-target range would require a sample size of 350 participants. Due to our definition of neonatal hypoglycaemia, we may also have underestimated the number of babies who were managed supportively with increased feeds or formula top-up feeds. Additionally, this is an observational analysis, and while we evaluated potential confounders, residual confounding may exist. This is particularly relevant for the apparent association between antenatal insulin pump therapy and neonatal hypoglycaemia, which is confounded by differences in maternal characteristics and glucose control between women using pumps or multiple daily injections (26). Finally, given the strong correlations between HbA_{1c} and other markers of glycaemia, the findings presented in Table 4 should not be interpreted to mean that it is only HbA_{1c} that is associated with neonatal hypoglycaemia.

It is clear that antepartum glycaemic control in the second and third trimesters is potentially modifiable and that even modest improvements are associated with a decreased risk of neonatal hypoglycaemia. Efforts should be focused on helping more women with Type 1 diabetes to improve glycaemic control throughout pregnancy so that the consequences of preterm birth and neonatal adiposity can be minimized. The high risk of neonatal hypoglycaemia in infants delivered before 37 weeks has important implications in terms of resource utilization, separation of infant mother pairs, and the long-term impact of neonatal hypoglycaemia into childhood. Further research into understanding the mechanisms, management and longer term consequences of neonatal hypoglycaemia, especially among preterm infants and extreme large for gestational age term infants of mothers with suboptimal glucose control, is required.

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Competing interests

RC reports advisory/personal fees from Roche, NovoNordisk, Sanofi and Lilly. DSF reports advisory/speaker fees from Medtronic, NovoNordisk and Dexcom. HRM reports personal fees from NovoNordisk, Roche, Medtronic and Abbott Diabetes Care, outside the current work. HRM sits on the Medtronic European Scientific Advisory Board.

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References

1. Yamamoto JM, Benham J, Mohammad K, Donovan LE, Wood S. Intrapartum glycaemic control and neonatal hypoglycaemia in pregnancies complicated by diabetes: a systematic review. *Diabet Med* 2018; **35:** 173–183.

2. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. *Neonatology* 2018; **115:** 116–126.

3. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ* 2004; **328:** 915.

4. Dashora U, Murphy HR, Temple RC, Stanley KP, Castro E, George S *et al*. Managing hyperglycaemia during antenatal steroid administration, labour and birth in pregnant women with diabetes. *Diabet Med* 2018; **35:** 1005–1010.

5. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period 25 February 2015. Available at https://www.nice.org.uk/guidance/ng3.

6. Diabetes Canada Clinical Practice Guidelines Expert Committee, Feig DS, Berger H, Donovan L, Godbout A, Kader T *et al*. Diabetes and Pregnancy. *Can J Diabetes* 2018; **42**(Suppl 1): S255–S282.

7. Levy N, Hall GM. National guidance contributes to the high incidence of inpatient hypoglycaemia. *Diabet Med* 2019; **36:** 120–121.

8. Modi A, Levy N, Hall GM. 'Primum non nocere' (first do no harm). Intrapartum glycaemic control and neonatal hypoglycaemia. *Diabet Med* 2018; **35:** 1130–1131.

9. Yamamoto JM, Murphy HR. Inpatient hypoglycaemia; should we should we focus on the guidelines, the targets or our tools? *Diabet Med* 2019; **36:** 122–123.

10. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C *et al*. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics* 2010; **126:** e1545–e1552.

11. Maresh MJ, Holmes VA, Patterson CC, Young IS, Pearson DW, Walker JD *et al*. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. *Diabetes Care* 2015; **38:** 34–42.

12. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF *et al*. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017; **390:** 2347–2359.

13. Stewart ZA, Yamamoto JM, Wilinska ME, Hartnell S, Farrington C, Hovorka R *et al*. Adaptability of closed loop during labor, delivery, and postpartum: a secondary analysis of data from two randomized crossover trials in type 1 diabetes pregnancy. *Diabetes Technol Ther* 2018; **20:** 501–505.

14. Stewart ZA, Thomson L, Murphy HR, Beardsall K. A feasibility study of paired continuous glucose monitoring intrapartum and in the newborn in pregnancies complicated by type 1 diabetes. *Diabetes Technol Ther* 2019; **21:** 20–27.

15. Gardosi J, Francis A. Gestation network. Customised weight centile calculator. GROW v 8.1 UK. Available at http://www.gestation.net/birthweightcentiles/centile_object.htm. Last accessed 7 July 2017.

16. Institute of Medicine and National Research Council of the National Academies. Weight gain during pregnancy: reexamining the guidelines 2009. Available at http://www.nationalacademies.org/hmd/~/media/Files/Report Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report Brief - Weight Gain During Pregnancy.pdf. Last accessed 11 January 2019.

17. Joshi T, Oldmeadow C, Attia J, Wynne K. The duration of intrapartum maternal hyperglycaemia predicts neonatal hypoglycaemia in women with pre-existing diabetes. *Diabet Med* 2017; **34:** 725–731.

18. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP *et al*. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. *N Engl J Med* 2016; **375:** 644–654.

19. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM *et al*. Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. *Diabetes Care* 2018; **41:** 1391–1399.

20. Drever E, Tomlinson G, Bai AD, Feig DS. Insulin pump use compared with intravenous insulin during labour and delivery: the INSPIRED observational cohort study. *Diabet Med* 2016; **33:** 1253–1259.

21. Yamamoto JM, Kallas-Koeman MM, Butalia S, Lodha AK, Donovan LE. Large-for-gestational-age (LGA) neonate predicts a 2.5-fold increased odds of neonatal hypoglycaemia in women with type 1 diabetes. *Diabetes Metab Res Rev* 2017; **33**.

22. Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER. Real-time continuous glucose monitoring during labour and delivery in women with Type 1 diabetes - observations from a randomized controlled trial. *Diabet Med* 2013; **30:** 1374–1381.

23. Group HSCR, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U *et al*. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358:** 1991–2002.

24. Hegarty JE, Harding JE, Gamble GD, Crowther CA, Edlin R, Alsweiler JM. Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: a randomised controlled dose-finding trial (the Pre-hPOD Study). *PLoS Med* 2016; **13:** e1002155.

25. Stenninger E, Lindqvist A, Aman J, Ostlund I, Schvarcz E. Continuous subcutaneous glucose monitoring system in diabetic mothers during labour and postnatal glucose adaptation of their infants. *Diabet Med* 2008; **25:** 450–454.

26. Feig DS, Corcoy R, Donovan LE, Murphy KE, Barrett JFR, Sanchez JJ *et al*. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial. Diabetes Care 2018; **41:** 2471–2479.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Table S1 Differences in cord blood C-peptide concentration (pmol/l) by neonatal and maternal characteristics.

Table S2 Results of univariate logistic regression for neonatal hypoglycaemia.

TABLE 1 Maternal and neonatal characteristics of offspring with and without neonatal hypoglycaemia

Variable	Neonatal hypoglycaemia	No neonatal hypoglycaemia	*P*-value
	N = 57	*N* = 168	
Maternal characteristics			
Age (years)	30.5 ± 4.6	31.7 ± 4.5	0.09
Duration of diabetes (years)	17.2 ± 7.6	16.3 ± 7.7	0.79
Diabetes complications*	11 (19)	47 (28)	0.20
Insulin pump use	**35 (61)**	**75 (45)**	**0.03**
Insulin pump during labour and delivery	13 (23)	33 (20)	0.61
Education (post-secondary)	42 (75)	132 (79)	0.58
Smoking during pregnancy	4 (7)	16 (10)	0.57
Primiparous	21 (37)	68 (40)	0.63
BMI (kg/m^2)	25.7 ± 4.5	25.8 ± 4.6	0.83
Preconception folic acid	29 (51)	87 (52)	0.91
Antenatal steroids	20 (35)	38 (23)	0.06
Antenatal glycaemia**			
First trimester			
HbA_{1c} (mmol/mol)	52 ± 6	52 ± 7	0.74
HbA_{1c} (%)	6.9 ± 0.6	6.9 ± 0.6	0.74
At target HbA_{1c}*** (mmol/mol) (%)	18 (35)	47 (30)	0.55
Time in target range (%)	49 ± 13	52 ± 13	0.12
Time above target (%)	42 ± 14	39 ± 14	0.14
Second trimester			
HbA_{1c} (mmol/mol)	**48 ± 7**	**45 ± 7**	**0.0009**
HbA_{1c} (%)	**6.6 ± 0.6**	**6.2 ± 0.6**	**0.0009**
At target HbA_{1c} (mmol/mol) (%)	**32 (58)**	**113 (72)**	**0.07**
Time in target range (%)	**46 ± 14**	**53 ± 15**	**0.004**

Time above target (%)	**50 ± 16**	**42 ± 17**	**0.002**
Third trimester			
HbA_{1c} (mmol/mol)	**50 ± 7**	**46 ± 7**	**0.0001**
HbA_{1c} (%)	**6.7 ± 0.6**	**6.3 ± 0.6**	**0.0001**
At target HbA_{1c} (mmol/mol) (%)	**18 (35)**	**105 (70)**	**< 0.0001**
Time in target range (%)	**60 ± 16**	**66 ± 14**	**0.03**
Time above target (%)	**35 ± 16**	**29 ± 14**	**0.01**
Neonatal characteristics			
Caesarean delivery	**47 (83)**	**108 (64)**	**0.01**
Gestational age (weeks)	**36.2 ± 1.7**	**37.2 ± 1.6**	**0.0002**
Preterm birth (< 37 weeks)	**36 (63)**	**53 (32)**	**< 0.0001**
NICU admission	**51 (90)**	**32 (19)**	**< 0.0001**
Birthweight (g)	3705 ± 819	3543 ± 659	0.13
Birthweight centile	**89 ± 22**	**80 ± 26**	**0.02**
SGA < 10th centile	1 (2)	3 (2)	1.0
LGA > 90th centile	**42 (74)**	**97 (58)**	**0.03**
Extreme LGA > 97.7th centile	**36 (63)**	**57 (34)**	**< 0.0001**
Exclusive breastfeeding at discharge	**18 (32)**	**83 (50)**	**0.02**

Data are presented as *n* (percentages) or means ± SD.

*Defined as any retinopathy, neuropathy or nephropathy.

**HbA_{1c} available for *n* = 52–55 mothers of infants with and *n* = 156–158 without neonatal hypoglycaemia; for continuous glucose monitoring data, *n* = 43–57 for mothers of infants with and *n* = 133–168 without neonatal hypoglycaemia.

***Target HbA_{1c} defined as < 48 mmol/mol (6.5%).

LGA, large for gestational age; NICU, neonatal intensive care unit; SGA, small for gestational age.

TABLE 2 Intrapartum continuous glucose monitoring (CGM) measures of maternal glycaemic control by offspring with and without neonatal hypoglycaemia

Glucose parameter	Neonatal hypoglycaemia	No neonatal hypoglycaemia	*P*-value
	N = 9	*N* = 24	
Time in target range (%)	76 (71, 83)	82 (59, 92)	0.82
Time above target range (%)	15 (12, 24)	17 (5, 33)	0.89
Time below target range (%)	0 (0, 3)	0 (0, 3)	0.67
Last blood glucose concentration prior to delivery (mmol/l)	5.7 (5.2, 7.9)	5.6 (5.3, 8.3)	0.89
Mean blood glucose concentration in labour and delivery (mmol/l)	6.4 (5.6, 7.0)	6.4 (5.8, 7.0)	0.81
SD (mmol/l)	1.4 (0.8, 1.8)	1.7 (1.1, 2.3)	0.11
Coefficient of variation (%)	22.2 (14.8, 32.3)	26.1 (20.4, 31.1)	0.28

Data are presented as medians (IQR); target defined as 3.5–7.8 mmol/l.

Intrapartum use of CGM was not required by the CONCEPTT study protocol, therefore glucose monitoring during labour and delivery was determined by participants and local healthcare teams. Data were available for 33 CONCEPTT participants (29 real-time CGM, 4 masked CGM)

TABLE 3 Neonatal adiposity and cord blood C-peptide concentration in offspring with and without neonatal hypoglycaemia

Variable	Neonatal hypoglycaemia	No neonatal hypoglycaemia	*P*-value
Skinfold measurements (mm)	*N* = 27	*N* = 123	
Triceps	6.8 ± 1.9	5.8 ± 1.7	0.004
Biceps	5.8 ± 1.4	4.9 ± 1.4	0.005
Subscapular	6.5 ± 1.5	5.7 ± 1.6	0.02
Flank (suprailiac)	6.0 ± 1.9	5.1 ± 1.8	0.02
	N = 38	*N* = 102	
Cord blood C-peptide concentration (pmol/l)	1416 (834, 2757)	662 (417, 1086)	< 0.00001
Cord blood C-peptide concentration > 566 pmol/l	33 (87)	59 (58)	0.001

Data are presented as *n* (percentages), means ± SD, or median (IQR). Skinfold measurements were available for 150 neonates. Cord blood C-peptides were available for *n* = 143 neonates. Cord C-peptide > 566 pmol/l is based on > 90th percentile value (> 1.7 ug/l) in the HAPO study

TABLE 4 Results of multivariable logistic regression for neonatal hypoglycaemia

	Unadjusted*	
	Odds ratio (95% CI)	*P*-value
All neonates		
Extreme large for gestational age > 97.7th centile	2.5 (1.3, 5.0)	0.007
Third trimester HbA_{1c} (mmol/mol) (per 1%)	2.3 (1.4, 4.0)	0.002
Term neonates**		
Extreme large for gestational age > 97.7th centile	**6.2 (1.8, 21.0)**	**0.003**
Third trimester HbA_{1c} (mmol/mol) (per 1%)	**3.5 (1.4, 9.0)**	**0.01**
Preterm neonates		
Extreme large for gestational age > 97.7th centile	1.3 (0.5, 3.2)	0.57
Third trimester HbA_{1c} (mmol/mol) (per 1%)	1.2 (0.6, 2.5)	0.58

*Smoking, diabetes duration and education did not confound the above models and therefore the unadjusted model is presented [term neonates: extreme large for gestational age and third trimester HbA_{1c} adjusted odds ratios (ORs) range from 6.1–6.2 and 3.4–3.6, respectively, and in preterm neonates: extreme large for gestational age and third trimester HbA_{1c} adjusted ORs were 1.3 and 1.2, respectively].

**Analysis stratified by preterm delivery (*P*-value for interaction term = 0.02).