Maternal Glycaemic Control and Risk of Neonatal Hypoglycaemia in Type 1 Diabetes Pregnancy– A secondary analysis of the CONCEPTT Trial

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Novelty Statement

- Neonatal hypoglycaemia is a common complication of type 1 diabetes pregnancy.
- We found that 15% of term and 40% of preterm infants had clinically relevant neonatal hypoglycaemia requiring treatment with intravenous dextrose.
- Modest differences in continuous glucose monitoring (CGM) time-in-target (5-7% increase) and HbA1c (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 (CGM) 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 CGM 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 HbA1c (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 CGM time-in-range (45.9% vs 53.0%; p=0.004 and 60.1% vs 65.7%; p=0.03). Neonates with hypoglycaemia had higher cord blood C-peptide (1416 [834, 2757] vs 662 [417, 1086] pmol/L; p<0.00001), birthweight >97.7th centile (63.2% vs 33.9%; p<0.0001) and skinfold thickness (p≤0.02). Intrapartum CGM was available for 33 participants, with no differences between mothers of neonates with and without hypoglycaemia.

Conclusions: Modest increments in CGM time-in-target (5-7% increase) during the second and third trimesters are associated with reduced risk for neonatal hypoglycaemia. While more intrapartum CGM 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.

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 (NICU), 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 (NICE) and Canadian guidelines recommend tight intrapartum glucose targets (4.0 to 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 Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated strong, continuous associations of maternal glucose levels at 24-32 weeks with neonatal hypoglycaemia. The HAPO investigators also demonstrated that birthweight >90th centile and higher percentage of body fat were associated with increased risk of neonatal hypoglycaemia. Maternal hyperglycaemia throughout pregnancy may be of greater importance than short duration intrapartum glucose control. The staff administering complex insulin regimens in labour and delivery units may have limited diabetes training, so 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).

CONCEPTT (Continuous Glucose Monitoring in Type 1 Diabetes Pregnancy Trial) was a multicentre trial, which randomised women to real-time continuous glucose monitoring (CGM) or standard capillary glucose monitoring (10). It described significantly less neonatal hypoglycaemia in infants of women randomised to CGM compared to 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 glycemic 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.

Participants and Methods

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 (10). In brief, CONCEPTT was a multicentre randomised 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 randomised to CGM or capillary glucose monitoring. Women randomised 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.

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 (11, 12) 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 glycemic variability measures (SD, CV)) during the 24 hours were assessed. Target range both antepartum and intrapartum was defined as 3.5 to 7.8 mmol/L.

The primary outcome of interest was clinical neonatal hypoglycaemia 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 Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study were used (13). Fetal anthropometric measures (triceps, sub scapular, biceps and suprailiac skin-folds) 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 (14).

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 and/or those available at time of delivery was included in the final model. We assessed for effect modification by preterm delivery using a likelihood-ratio test and a stratified analysis was performed when modification was identified. Additionally, adjustment for potential confounders including smoking, diabetes duration and education level was performed using multiple logistic regression. Results are presented as OR (95% confidence intervals [CI]). All analyses were performed using STATA (Stata Corp. LP, College Station, TX, Version 14.1). A two-sided p-value of <0.05 was considered statistically significant.

Results

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

Neonatal hypoglycaemia occurred in 57 (25.3%) 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, admitted to NICU and less likely to be exclusively breastfed at discharge. They had higher customised birthweight percentile, and higher rates of large and extreme large for gestational age.

Antepartum glycaemic control

There were no differences in HbA1c 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 HbA1c levels, less time spent in the target glucose range, and more time-above-target both at 24 and at 34 weeks gestation.

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, HbA1c or pump use, in women who continued CGM intrapartum compared to 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 randomised to CGM than to capillary glucose monitoring (87.9 vs 12.1%; 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.

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 (13).

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 UK, Canada, Ireland or the United States compared to 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 a HbA1c <6.5%, compared to those that did not (Table S1). Post hoc analyses revealed no difference in cord C-peptide levels of women who were overweight compared to women with normal weight in early pregnancy. There was also no difference in cord C-peptide levels in women with excessive compared to appropriate gestational weight gain defined by the Institute of Medicine guidelines (15). 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 (sum of 4 skin folds (triceps, subscapular, biceps, flank) 24.5 ± 5.7 vs 19.2 ± 3.8 mm respectively; p<0.00001).

Logistic regression analysis

Univariate logistic regression identified gestational age at delivery, large and extreme large for gestational age, antenatal glycaemia (2nd and 3rd trimester HbA1c and CGM measures), insulin pump use, caesarean delivery, and cord blood C-peptide as being significantly associated with neonatal hypoglycaemia (Table S2).

When developing the model, 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). In term neonates, extreme large for gestational age

(adjusted OR 6.1 [95% CI 1.8, 20.7]; p=0.004) and 3rd trimester HbA1c (adjusted OR 3.5 [95% CI 1.3, 9.7]; p=0.02) were significantly associated with increased odds of neonatal hypoglycaemia in both the unadjusted analysis and the analysis adjusted for smoking, diabetes duration and education level (Table 4). However, in preterm neonates, neither extreme large for gestational age (adjusted OR 1.2 [95% CI 0.5, 3.1]; p=0.65) nor 3rd trimester HbA1c (adjusted OR 1.2 [95% CI 0.6, 2.4]; p=0.67) were significantly associated with increased odds of neonatal hypoglycaemia.

Discussion

Maternal antenatal glucose control, as measured by HbA1c 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 0.4% decrease in HbA1c 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 glycemic control, genetic, dietary and environmental

factors (10). The HAPO investigators previously demonstrated that the odds of neonatal hypoglycaemia increased in a graded way with increasing cord blood C-peptide levels (13). 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 HbA1c 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 (16, 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 odds ratio for neonatal hypoglycaemia (15 vs 28%; p=0.03). Both women with and without neonatal hypoglycaemia spent more time in target range in the intrapartum period (76.0 and 81.8% respectively) compared to 34 weeks gestation (60.1 and 65.7% respectively). This is consistent with the closed-loop studies in pregnancy which demonstrate a higher time in target in the intrapartum period compared to earlier in pregnancy (11, 18, 19).Whist 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, be

more resource efficient than intravenous insulin regimens and preferable for women to manage their own diabetes (11).

We also found extreme large for gestational age was associated with a 6-fold increased odds of neonatal hypoglycaemia in term neonates. This increased risk of neonatal hypoglycaemia seen 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, 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 characterise intrapartum glycaemic control (11, 12, 22, 25). A pilot study evaluating closed-loop during labour and delivery (n=27 participants) found comparable intrapartum glycaemia (82% time in target range) to CONCEPTT participants without neonatal hypoglycaemia, also with no between group differences according to the presence or absence of neonatal hypoglycaemia (11). 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) (12). 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 two 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 two hours of suboptimal glycaemia. Large, high quality, randomised controlled trials of strict vs more relaxed intrapartum targets would be needed to determine if the benefits of strict glycemic control during this period outweigh the risks in women with type 1 diabetes.

Our study has several strengths. It is a large, multicentre, well characterised cohort of women with type 1 diabetes with detailed information regarding glycaemic control as assessed by both HbA1c and CGM. The data were prospectively collected and rigorously evaluated with standardised central laboratory HbA1c 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 adjusted and evaluated for 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 HbA1c and other markers of glycaemia, the findings presented in Table 4 should not be interpreted to mean that it is only HbA1c that is associated with neonatal glycemia.

It is clear that antepartum glycaemic control in the second and third trimesters is potentially modifiable and that even modest improvements are associated with decreased risk of neonatal hypoglycaemia. Efforts should focus 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 minimised. The high risk of neonatal hypoglycaemia in infants delivered before 37 weeks, has important implication 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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Conflicts of Interest

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

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Contribution

JMY, RC, KB, DSF and HRM conceived and designed the study. RC, LED, ZAS, DSF, HRM collected the data. JMY analysed the data. JMY, RC, KB and HRM interpreted the data. JMY and HRM prepared the manuscript, which all authors critically reviewed. All authors have given

final approval of the version to be published. JMY is the guarantor of this work, had full access to all the study data and takes responsibility for the integrity of the data.

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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 & 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
Pre-conception folic acid	29 (51)	87 (52)	0.91
Antenatal steroids	20 (35)	38 (23)	0.06
Antenatal Glycaemia**			
First Trimester			
HbA1c (%)	6.9 ± 0.6	6.9 ± 0.6	0.74
HbA1c (mmol/mol)	52 ± 6	52 ± 7	0.74
At target HbA1c***	18 (35)	47 (30)	0.55
Time in target range (%)	49.3 ± 12.8	52.4 ± 13.1	0.12
Time above target (%)	42.3 ± 14.0	39.1 ± 14.3	0.14
Second Trimester			
HbA1c (%)	**6.6 ± 0.6**	**6.2 ± 0.6**	**0.0009**
HbA1c (mmol/mol)	**48 ± 7**	**45 ± 7**	**0.0009**
At target HbA1c	**32 (58)**	**113 (72)**	**0.07**
Time in target range (%)	**45.9 ± 14.5**	**53.0 ± 15.1**	**0.004**
Time above target (%)	**49.8 ± 16.4**	**41.6 ± 16.6**	**0.002**
Third Trimester			
HbA1c (%)	**6.7 ± 0.6**	**6.3 ± 0.6**	**0.0001**
HbA1c (mmol/mol)	**50 ± 7**	**46 ± 7**	**0.0001**
At target HbA1c	**18 (35)**	**105 (70)**	**<0.0001**
Time in target range (%)	**60.1 ± 15.7**	**65.7 ± 14.1**	**0.03**
Time above target (%)	**35.5 ± 16.5**	**29.0 ± 14.0**	**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 (grams)	3705 ± 819	3543 ± 659	0.13
Birthweight centile	**89.1 ± 21.5**	**80.3 ± 26.2**	**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 ± standard deviation. *Defined as any retinopathy, neuropathy or nephropathy; **HbA1c available for n=52 to 55 mothers of infants with and n=156 to 158 without neonatal hypoglycaemia; For CGM data n=43 to 57 for mothers of infants with and n=133 to 168 without neonatal hypoglycaemia; ***Target HbA1c defined as <6.5% (48 mmol/mol); SGA, small for gestational age; LGA large for gestational age; NICU, neonatal intensive care unit.

Table 2: Intrapartum Continuous Glucose Monitoring 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 (%)	76.0 (71.4, 83.0)	81.8 (58.8, 92.1)	0.82
Time above target range (%)	14.8 (11.5, 24.36)	16.8 (5.4, 33.2)	0.89
Time below target range (%)	0 (0, 2.8)	0 (0, 2.3)	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
Standard deviation (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 (interquartile range); 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 in 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)**	**<0.0001**
Cord blood C-peptide concentration>566 pmol/L \	**33 (87)**	**59 (58)**	**0.001**

Data are presented as n (percentages), means ± standard deviation, or median (interquartile range); 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		Adjusted*	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Term Neonates**				
Extreme LGA	**6.2 (1.8, 21.0)**	**0.003**	**6.1 (1.8, 20.7)**	**0.004**
3rd trimester HbA1c (per 1%)	**3.5 (1.4, 9.0)**	**0.01**	**3.5 (1.3, 9.7)**	**0.02**
Preterm Neonates				
Extreme LGA	1.3 (0.5, 3.2)	0.57	1.2 (0.5, 3.1)	0.65
3rd trimester HbA1c (per 1%)	1.2 (0.6, 2.5)	0.58	1.2 (0.6, 2.4)	0.67

*Adjusted model including extreme LGA, 3rd trimester HbA1c and smoking, diabetes duration, and education level stratified by preterm delivery; **Analysis stratified by preterm delivery (p-value for interaction term=0.02); LGA, large for gestational age