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Research: Pregnancy

Severe neonatal hypoglycaemia and intrapartum glycaemic control in pregnancies complicated by type 1, type 2 and gestational diabetes

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Abstract

Aims To determine if in-target intrapartum glucose control is associated with neonatal hypoglycaemia in women with type 1, type 2 or gestational diabetes.

Methods This was a retrospective cohort study of pregnant women with diabetes and their neonates. The primary exposure was in-target glucose control, defined as all capillary glucose values within the range 3.5–6.5 mmol/l during the intrapartum period. The primary outcome, neonatal hypoglycaemia, was defined as treatment with intravenous dextrose therapy. Multiple logistic regression was used to examine the association between maternal intrapartum glycaemic control and neonatal hypoglycaemia, adjusting for covariates.

Results Intrapartum glucose testing was available for 157 (86.3%), 267 (76.3%) and 3256 (52.4%) women with type 1, type 2 and gestational diabetes, respectively. In the univariate analysis, in-target glycaemic control was significantly associated with neonatal hypoglycaemia in women with gestational diabetes, but not in women with type 1 or 2 diabetes. However, after adjustment for important neonatal factors (large for gestational age, preterm delivery and infant sex), intrapartum in-target glycaemic control was not significantly associated with neonatal hypoglycaemia in women regardless of diabetes type [adjusted odds ratios 0.4 (95% CI 0.1, 1.4), 0.7 (95% CI 0.3, 1.3) and 0.7 (95% CI 0.5, 1.0) for women with type 1, type 2 and gestational diabetes, respectively].

Conclusions There was no significant association between in-target glycaemic control and neonatal hypoglycaemia after adjustment for neonatal factors. Given the high risk of maternal hypoglycaemia and the resources required, future trials should consider whether more relaxed intrapartum glycaemic targets may be safer and yield similar neonatal outcomes.

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Introduction

Diabetes continues to be a common complication in pregnancy worldwide [1]. Unfortunately, pregnancies in women with diabetes are associated with an increased risk of complications [2–4]. Neonatal hypoglycaemia is one such risk and is common in pregnancies with diabetes [4–6]. Its definition is quite contentious, but is generally based on a blood glucose level, signs of hypoglycaemia and/or need for treatment [4,7].

Current guidelines recommend intensive intrapartum glycaemic control (4.0–7.0 mmol/l) to decrease the risk of neonatal hypoglycaemia by preventing a rise in foetal insulin in the hours prior to delivery [8,9]. Tight glycaemic control is generally achieved through use of insulin therapy, administered subcutaneously or intravenously. This requires additional close monitoring throughout labour by the hospital staff, who often lack expertise in diabetes care. Furthermore, the risk of harm from maternal hypoglycaemia and increased resource utilization must also be weighed against the theoretical benefit of tight glycaemic control in labour and delivery.

There are clear risk factors associated with neonatal hypoglycaemia, such as preterm delivery and large-for-

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What's new?

- In pregnancies with diabetes, guidelines recommend tight intrapartum glycaemic control based on the theory that this will decrease the risk of neonatal hypoglycaemia; however, the evidence supporting this theory is conflicting.
- In this large cohort of women with type 1, type 2 and gestational diabetes, there was no significant association between in-target intrapartum glycaemic control and severe neonatal hypoglycaemia after adjustment for neonatal confounders.
- Future trials should consider whether more relaxed intrapartum glycaemic targets may be safer in women with diabetes in pregnancy and yield similar neonatal results or outcomes.

gestational-age infant [4,5,10]. Most studies examining intrapartum glycaemic control did not adjust for these factors which predate the short intrapartum period [11]. For example, in both type 1 and gestational diabetes, infant size and adiposity have been associated with neonatal hypoglycaemia [4,5,10]. As both are established prior to labour and delivery, it seems less likely that minor changes during the intrapartum period could substantially lower the risk of neonatal hypoglycaemia. Large high-quality studies are needed to address whether in-target intrapartum glycaemic control is associated with neonatal hypoglycaemia when considering important neonatal confounders.

Our aim was to determine if in-target glucose control during labour and delivery was associated with neonatal hypoglycaemia in women with type 1, type 2 or gestational diabetes after adjustment for neonatal confounders.

Methods

We performed a retrospective cohort study in pregnant women with type 1, type 2 or gestational diabetes and their neonates.

Study population

Information was collected on consecutive women with type 1, type 2 or gestational diabetes who attended specialized interdisciplinary clinics between 1 January 2007 and 31 December 2014 in four tertiary care hospitals in Calgary, Canada. Calgary is a city with an ethnically diverse population of ~1.4 million [12].

For inclusion in the study, women were required to have a preconception diagnosis of diabetes or a diagnosis of gestational diabetes. Women were excluded if they had delivered outside of the study area, had an unclear definition of type of diabetes, had an unknown expected date of confinement, or delivered after the study period. Women who had a multiple gestation pregnancy were included in the analysis. For women with multiple pregnancies during the study period or a multiple gestation, one pregnancy or neonate was randomly chosen for inclusion.

Data sources and collection

Demographic and outcome data were obtained through multiple databases including the Alberta Perinatal Health Program database, the Analytics database, the Sunrise Clinical Management system, the Diabetes in Pregnancy clinical database, and laboratory information systems for Calgary, Central and South Zone, all linked by a unique identification number.

Most neonatal outcome and pregnancy data were obtained from the Alberta Perinatal Health Program. This database (www.aphp.ca) includes information collected on the provincial delivery record regarding pregnancy, delivery and neonatal outcome data for all hospital and registered midwife-attended home births in Alberta, Canada. Details on the type of diabetes and treatment of diabetes were obtained from the diabetes in pregnancy clinical database used at all four tertiary care diabetes-in-pregnancy clinics. The Diabetes in Pregnancy clinical database is a clinical record used by doctors, nurses and dietitians who provide diabetes care to pregnant women.

In-hospital maternal glucose values, maternal insulin use during labour and delivery, and intravenous dextrose treatment of neonates were obtained using the provincial health services Analytics database and the Sunrise Clinical Management system (an electronic health record used at all four hospitals). Laboratory data regarding antenatal glycaemic control were obtained from the laboratory information systems for Calgary, Central and South Zone. Information on neonates was obtained by using their unique identification number identified by the delivery record and from the Alberta Perinatal Health Program database. The data source for each variable is summarized in Table S1.

Local guidelines

All women with diabetes should undergo a capillary glucose test at the onset of active labour [13]. For women with type 1 and 2 diabetes, glucose testing is recommended every 1 h during active labour. For women with gestational diabetes, if they have a glucose level < 6.5 mmol/l in active labour, no additional testing, insulin, or endocrine consultation is required. If women with gestational diabetes have two consecutive glucose values > 6.5 mmol/l, an endocrine consultation is recommended for consideration of insulin treatment. Anyone receiving intravenous insulin infusion requires hourly capillary glucose monitoring regardless of the type of diabetes.

Local guidelines for the screening and management of neonatal hypoglycaemia recommend that all neonates of mothers with diabetes be screened with a point-of-care blood glucose, immediately if symptomatic, or up to 1 h after the

first feed if asymptomatic [14]. Subsequent glucose testing is dependent on initial glucose value. It is recommended that repeat glucose testing is performed until glucose stability is achieved in all infants at risk of hypoglycaemia. In infants of mothers with diabetes, blood glucose monitoring is required until up to 12 h of age.

Definitions and outcome measures

The primary exposure of interest was intrapartum maternal glycaemic control. The a priori definition of in-target glucose control was having all intrapartum capillary blood glucose values within the range 3.5–6.5 mmol/l. This was based on local clinical practice guidelines which were based on the Canadian Diabetes Association 2008 Clinical Practice Guideline recommendations [15]. The intrapartum period was defined as up to 24 h prior to delivery, in keeping with the recent literature [10,16,17]. We also examined the a priori outcomes of proportion of glucoses in-target (50% and 25% between 3.5 and 6.5 mmol/l), and overt hyperglycaemia in labour (i.e. glucose values ≥ 8.6 mmol/l). Maternal hypoglycaemia during labour and delivery was defined as any recorded glucose of < 3.5 mmol/l.

Type of diabetes was determined based on the diagnosis entered by the diabetes in pregnancy clinicians into the clinical database. For women who were seen in the diabetes in pregnancy clinic with an uncertain diagnosis of diabetes, chart review was performed to determine the type of diabetes. Additional maternal characteristics collected included: maternal age at time of delivery, parity, pre-pregnancy weight > 91 kg (which is available on the prenatal record), smoking during pregnancy, pre-existing and gestational hypertension (defined as a systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg on at least two occasions > 6 h apart after 20 weeks' gestation, with no other maternal organ dysfunction), diabetes medication, and insulin use. Trimester-specific HbA_{1c} was defined as the mean HbA_{1c} for each trimester (conception to 12+6 weeks, first trimester; 13 to 27+6 weeks, second trimester; and 28 weeks to term, third trimester).

Our a priori primary outcome, neonatal hypoglycaemia, was defined as treatment of the neonate with intravenous dextrose therapy. Additional neonatal outcome data included: sex; mode of delivery; birth gestational age; admission to the neonatal intensive care unit; preterm delivery (< 37 weeks' gestation); very preterm delivery (< 34 weeks' gestation); birth weight; and size for gestational age. Neonates were defined as large for gestational age and extremely large for gestational age if their birth weight was > 90th and > 97th percentile, respectively, based on national population references for age and sex [18].

Statistical analysis

Data were compared using chi-squared tests for categorical variables and *t*-tests for continuous variables. An a priori decision was made to stratify analyses by type of diabetes (type 1, type 2 and gestational). Multiple logistic regression was used to examine the association between maternal in-target intrapartum glycaemic control and neonatal hypoglycaemia, adjusting for covariates. In the development of the final regression models, we assessed for effect modification by preterm delivery and large for gestational age using a likelihood ratio test. The univariate analysis, existing literature and clinical knowledge were used to inform model variable choice. Additionally, we considered the number of neonates with hypoglycaemia when deciding on included variables to avoid over-fitting of the models. In cases of variable multicollinearity, the variable with the strongest association across the types of diabetes was included. All analyses were performed using STATA (Stata Corp. LP, College Station, TX, USA, Version 14.1). P values < 0.05 were taken to indicate statistical significance.

Ethics

Ethics approval was obtained from the Conjoint Heath Research Ethics Board, University of Calgary (REB16-2093). The study protocol was registered online prior to obtaining the data (https://osf.io/37edr/).

Results

After database merging, removal of pregnancies not meeting inclusion criteria and the random selection of one pregnancy or neonate per woman, 8451 mother–infant pairs were identified (Fig. 1). Because the primary exposure, intrapartum glycaemic control, was missing for > 90% of pregnancies in 2007 and 2008 only, but missing data were stable for the years thereafter, it is likely that charting on the electronic system was not routinely carried out until 2009. We therefore chose to exclude pregnancies prior to 2009. A total of 6740 maternal infant pairs were included in the present cohort study and 3680 maternal infant pairs were included in the intrapartum glycaemic control analysis (Fig. 1).

Maternal characteristics by type of diabetes are shown in Table 1. Of the 6740 women included, 182 had type 1 diabetes, 350 had type 2 diabetes and 6208 had gestational diabetes. The number of infants with neonatal hypoglycaemia was 50 (27.5%), 64 (18.3%) and 313 (5.0%) for women with type 1, type 2 and gestational diabetes, respectively. Detailed neonatal characteristics are shown in Table 2.

Intrapartum glycaemic control

Intrapartum glucose testing was available for 157 (86.3%), 267 (76.2%) and 3256 (52.4%) women with type 1, type 2 and gestational diabetes, respectively. To ensure there were no intrapartum glycaemic control data lost from database

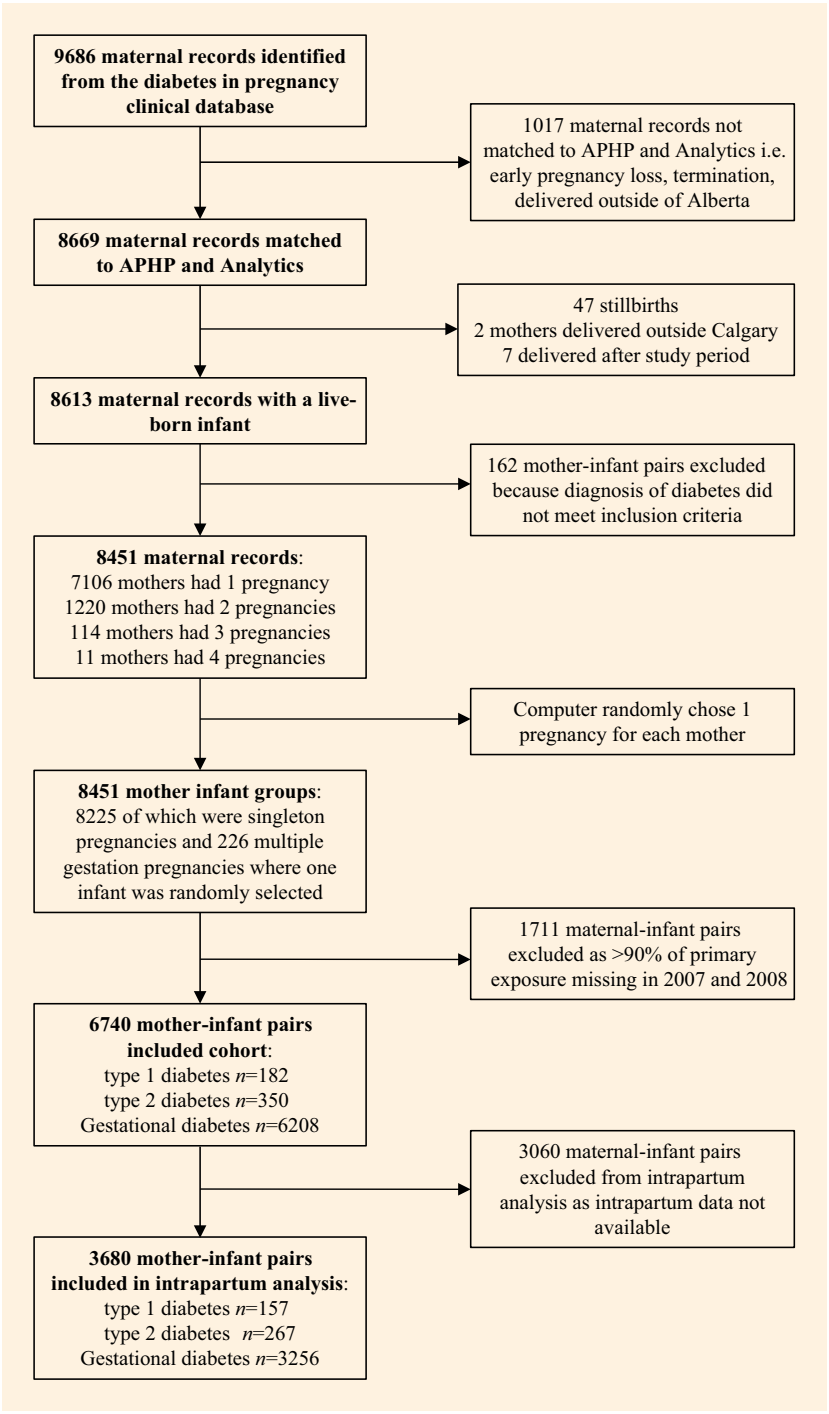

FIGURE 1 Flow diagram of mother–infant pairs included in the study cohort. APHP, Alberta Perinatal Health Program.

extraction, the charts of women who had type 1 diabetes and no intrapartum glucose data (n = 25) were all reviewed. It was confirmed that none of those women had glucose data recorded prior to delivery.

We analysed the data to identify important differences between women with and without intrapartum testing (Table S2). Women with type 1 diabetes with and without intrapartum glycaemic control data did not significantly differ. Women with type 2 diabetes who had undergone intrapartum testing had significantly lower third trimester HbA_{1c} values than women who had not [45 ± 9 vs. 49 ± 11 mmol/mol (6.3 ± 0.8 vs. 6.6 ± 1.0%) respectively; $P = 0.007$], but did not differ otherwise. Women with gestational diabetes who underwent intrapartum testing

Table 1 Maternal characteristics by type of diabetes

	type 1 diabetes n = 182	type 2 diabetes n = 350	Gestational diabetes n = 6208
Maternal characteristic*			
Maternal age, years	30.1 ± 5.0	33.7 ± 5.0	33.0 ± 4.9
Duration of diabetes, years	14.9 ± 8.4	4.0 ± 4.2	–
Primiparous	108 (59.3)	127 (36.3)	2469 (39.8)
Pre-pregnancy weight > 91 kg	16 (8.8)	126 (36.0)	742 (12.0)
Smoker	24 (13.2)	35 (10.0)	384 (6.2)
Pre-existing hypertension	3 (1.7)	21 (6.0)	85 (1.4)
Pregnancy-induced hypertension	39 (21.4)	65 (18.6)	626 (10.1)
Insulin pump	55 (30.2)	1 (0.3)	0 (0)
Insulin use	182 (100)	314 (89.7)	1953 (31.5)
Metformin	3 (1.7)	106 (30.3)	94 (1.5)
Other oral diabetes medications	0 (0)	10 (2.9)	1 (0.02)
Intrapartum intravenous insulin infusion	111 (61.0)	58 (16.6)	61 (1.0)
Maternal glycaemic control*			
HbA_{1c}			
1st trimester, mmol/mol	60 ± 16	54 ± 16	–
1st trimester, %	7.6 ± 1.4	7.1 ± 1.5	–
2nd trimester, mmol/mol	51 ± 10	45 ± 9	
2nd trimester, %	6.8 ± 0.9	6.3 ± 0.8	–
3rd trimester, mmol/mol	52 ± 9	46 ± 9	
3rd trimester, %	6.9 ± 0.8	6.3 ± 0.9	–
Glucose screen (50 g)			
1-h glucose, mmol/l			9.6 ± 1.6
Oral glucose tolerance test (75 g)			
Fasting glucose, mmol/l	–	–	4.8 ± 0.8
1-h glucose, mmol/l	–	–	10.7 ± 1.3
2-h glucose, mmol/l	–	–	9.0 ± 1.5

Data are presented as counts (percentages) and means ± SD.
*Diabetes duration available for 173 women with type 1 diabetes and 314 women with type 2 diabetes. Parity missing on six records. Smoking and hypertension missing on nine records.
*Trimester-specific HbA_{1c} value was available for 160–173 women and 241–290 women with type 1 and type 2 diabetes, respectively. Glucose screen data were available for 5664 women with gestational diabetes. Oral glucose tolerance test data were available for 3476–4259 women with gestational diabetes.

compared with those who did not were younger (32.8 ± 4.9 vs. 33.2 ± 4.9 years; $P = 0.0007$), more likely to be on insulin (42.3% vs. 19.5%; $P < 0.0001$) and had slightly higher fasting, 1-h and 2-h glucose values on a 75-g oral glucose tolerance test. They were slightly more likely to have a neonate with hypoglycaemia (5.6% vs. 4.4%; $P = 0.04$), although did not differ in other neonatal characteristics.

Of the women with capillary glucose testing, the mean number of capillary glucose tests performed for those with type 1, type 2 and gestational diabetes was 9.8 ± 7.6, 4.9 ± 4.7 and 1.8 ± 1.6, respectively. Hypoglycaemia during the intrapartum period (defined as at least one recorded glucose < 3.5 mmol/l) was more common in women with type 1 diabetes, with 56 of 157 (35.7%) women compared to 38 of 267 (14.2%) and 78 of 3256 (2.4%) women with type 2 and gestational diabetes, respectively.

Intrapartum glycaemic control and neonatal hypoglycaemia

There was no significant difference in our primary exposure, in-target glucose control, between women with type 1 and type 2 diabetes who had neonates with and without hypoglycaemia (3). In women with gestational diabetes, however, those who had neonates with hypoglycaemia were less likely to have in-target glucose control compared to those whose neonates were without hypoglycaemia (69.8% vs. 78.4%, respectively; $P = 0.006$). A summary of the prespecified and exploratory intrapartum glycaemic variables between mothers of neonates with and without neonatal hypoglycaemia is found in Table 3.

Univariate analysis was used to examine associations between maternal and neonatal characteristics and neonatal hypoglycaemia (Table S3). In the group with type 1 diabetes, large-for-gestational-age and extremely large-for-gestational-age infants, preterm delivery, HbA_{1c} (first, second and third trimesters), male sex and maternal smoking were significantly associated with neonatal hypoglycaemia. In the group with type 2 diabetes, extremely large-for-gestational-age infant, preterm delivery, HbA_{1c} (second and third trimesters), caesarean section and pregnancy-induced hypertension were associated with neonatal hypoglycaemia. For women with gestational diabetes, large-for-gestational-age and extremely large-for-gestational-age infants, preterm delivery, 2-h oral glucose tolerance test glucose, pre-pregnancy weight > 91 kg, male sex, pregnancy-induced hypertension and intrapartum glycaemic control were associated with neonatal hypoglycaemia.

Table 2 Neonatal characteristics by type of diabetes

	type 1 diabetes n = 182	type 2 diabetes n = 350	Gestational diabetes n = 6208
Neonatal characteristic*			
Neonatal hypoglycaemia (i.v. dextrose)	50 (27.5)	64 (18.3)	313 (5.0)
Male sex	99 (54.4)	184 (52.6)	3257 (52.5)
Caesarean section	110 (60.4)	200 (57.1)	2336 (37.6)
Gestational age	36.5 ± 1.9	37.2 ± 1.8	38.2 ± 1.7
Preterm	74 (40.7)	69 (19.7)	674 (10.9)
Early preterm	9 (5.0)	15 (4.3)	126 (2.0)
Neonatal intensive care unit admission	101 (55.5)	108 (31.0)	871 (14.0)
Birthweight, g	3474 ± 678	3241 ± 681	3229 ± 552
Large for gestational age	88 (48.4)	83 (23.7)	602 (9.7)
Extremely large for gestational age	47 (25.8)	37 (10.6)	218 (3.5)
Small for gestational age	3 (1.7)	30 (8.6)	684 (11.0)

i.v., intravenous. Data are presented as counts (percentages) or means ± SD.
*Neonatal intensive care unit admission missing on six records; birthweight information missing on one record.

After adjustment for important neonatal factors (large-for-gestational-age infant, preterm delivery and infant sex), intrapartum in-target glycaemic control was not significantly associated with neonatal hypoglycaemia in women regardless of their type of diabetes (Table 4). Additionally, further adjustment for maternal glycaemic control (specifically mean second trimester HbA_{1c}) did not change the association between intrapartum in-target glycaemic control and neonatal hypoglycaemia in women with type 1 and type 2 diabetes [adjusted odds ratio 0.3 (95% CI 0.1, 1.2) and 0.7 (95% CI 0.3, 1.4), respectively].

Discussion

We report on the largest cohort examining the relationship between intrapartum glycaemic control and neonatal hypoglycaemia in women with diabetes in pregnancy. We found that neonatal hypoglycaemia was common in women with type 1 diabetes (28%) and type 2 diabetes (18%), but comparatively less common in women with gestational diabetes (5%). After adjustment for neonatal factors, there was no significant association between in-target intrapartum glycaemic control and neonatal hypoglycaemia regardless of the type of diabetes.

Our findings are consistent with some but not all studies examining the importance of glycaemic control during labour and delivery as the literature in this area is conflicting [11,19,20]. A recent systematic review highlighted the lack of high-quality studies supporting the association between intrapartum glycaemic control and risk of neonatal hypoglycaemia [11]. Authors noted that lack of adjustment for known confounders was common in studies that identified a consistent and significant association. It is important to note that, while our unadjusted analysis found significant associations between some intrapartum measures and neonatal hypoglycaemia, this significant association was no longer apparent after adjustment for known neonatal risk factors.

In contrast to our findings, a study by Joshi *et al.* [20] that included women with pre-existing diabetes (n = 247) found the percentages of intrapartum test values within the ranges 7–10 mmol/l (odds ratio 1.02; $P = 0.001$) and 4–7 mmol/l (odds ratio 0.99; $P = 0.02$) were associated with neonatal hypoglycaemia after adjustment for confounders [20]. The difference between their findings and those of the present study may be explained by the use of different definitions of neonatal hypoglycaemia. Joshi *et al.* used a neonatal glucose value of ≤ 2.6 mmol/l, whereas we used a definition of neonates requiring intravenous dextrose. It is unclear if the significant relationship found by Joshi *et al.* would persist if a more severe form of neonatal hypoglycaemia, such as need for intravenous dextrose therapy, was examined. Joshi *et al.* noted that, while this association was statistically significant, the magnitude was small. They also highlighted other factors such as antenatal glycaemic control that were associated with neonatal hypoglycaemia.

We found that antenatal glycaemic control, as assessed by HbA_{1c}, was associated with neonatal hypoglycaemia in women with pre-existing diabetes. This association between antenatal glycaemic control and neonatal hypoglycaemia has been found across populations [10,20,21]. This may be attributable to the direct effect of maternal antenatal hyperglycaemia on foetal hyperinsulinaemia or mediated through other outcomes associated with neonatal hypoglycaemia, such as preterm delivery and large-for-gestational-age infants [10,21]. Notably, our finding that large infant size was associated with neonatal hypoglycaemia in all types of diabetes is consistent with the available literature [5,10]. Both findings support the hypothesis that factors occurring well before parturition pose a more substantial risk for the occurrence of neonatal hypoglycaemia than intrapartum maternal glycaemic control.

Neonatal hypoglycaemia following pregnancies with gestational diabetes was relatively uncommon (5%) in the present study and consistent with the literature that used a

Table 3 Intrapartum (within 24 h prior to delivery) glycaemic control for mothers of neonates with and without hypoglycaemia by type of diabetes

	type 1 diabetes n = 157			type 2 diabetes n = 267			Gestational diabetes n = 3256		
	Neonatal hypoglycaemia n = 47	No neonatal hypoglycaemia n = 110	*P*	Neonatal hypoglycaemia n = 46	No neonatal hypoglycaemia n = 221	*P*	Neonatal hypoglycaemia n = 182	No neonatal hypoglycaemia n = 3074	*P*
Prespecified									
In-target glucose*	5 (10.6)	19 (17.3)	0.29	20 (43.5)	120 (54.3)	0.18	**127 (69.8)**	**2410 (78.4)**	**0.006**
Overt hyperglycaemia (≥ 8.6 mmol/l)	22 (46.8)	47 (42.7)	0.64	11 (23.9)	33 (14.9)	0.14	**18 (9.9)**	**116 (3.8)**	**< 0.0001**
At least 50% in target	31 (66.0)	73 (66.4)	0.96	**35 (76.1)**	**193 (87.3)**	**0.049**	**156 (85.7)**	**2786 (90.6)**	**0.03**
At least 25% in target	36 (76.6)	90 (81.8)	0.45	**37 (80.4)**	**203 (91.9)**	**0.02**	**160 (87.9)**	**2869 (93.3)**	**0.005**
Exploratory analyses									
Actionable glucose	38 (80.9)	87 (79.1)	0.80	21 (45.7)	87 (39.4)	0.43	**24 (13.2)**	**189 (6.2)**	**< 0.0001**
% of tests within target	53.6 ± 34.3	57.7 ± 31.8	0.47	**67.3 ± 36.7**	**78.5 ± 30.2**	**0.03**	**80.5 ± 33.9**	**86.9 ± 28.4**	**< 0.003**
% of tests above target	41.4 ± 35.7	36.7 ± 32.8	0.42	26.3 ± 35.7	18.1 ± 28.9	0.09	**18.4 ± 32.8**	**12.0 ± 27.4**	**0.003**
% of tests below target	5.0 ± 11.6	5.6 ± 9.2	0.73	6.4 ± 15.5	3.3 ± 11.8	0.13	1.2 ± 10.5	1.1 ± 8.2	0.87
% of tests ≥ 8.6 mmol/L	17.7 ± 29.5	13.9 ± 24.3	0.40	7.0 ± 13.3	4.0 ± 12.7	0.14	**5.7 ± 19.7**	**1.7 ± 10.1**	**< 0.00001**
Mean glucose, mmol/l	6.7 ± 2.9	6.4 ± 1.9	0.34	5.7 ± 1.5	5.6 ± 1.4	0.53	**5.7 ± 1.7**	**5.3 ± 1.4**	**0.006**
Last glucose, mmol/l	6.8 ± 3.1	6.1 ± 2.3	0.10	5.6 ± 1.4	5.4 ± 1.8	0.16	**5.5 ± 1.6**	**5.3 ± 1.3**	**0.03**

Data are presented as counts (percentages) or means ± SD.
Comparisons that are boldface type indicate statistically significant differences.
*Defined as all glucoses within target range of 3.5–6.5 mmol/l prior to delivery.

Table 4 Adjusted multivariable logistic regression models for neonatal hypoglycaemia

	Adjusted model Odds ratio (95% CI)	*P*
type 1 diabetes		
In-target glycaemic control	0.4 (0.1, 1.4)	0.18
Large for gestational age	**3.1 (1.5, 6.7)**	**0.004**
Preterm delivery	**4.1 (1.9, 8.9)**	**< 0.0001**
Male sex	2.0 (0.9, 4.5)	0.08
type 2 diabetes		
In-target glycaemic control	0.7 (0.3, 1.3)	0.23
Large for gestational age	1.7 (0.8, 3.6)	0.16
Preterm delivery	**2.1 (1.0, 4.5)**	**0.048**
Male sex	1.2 (0.6, 2.4)	0.52
Gestational diabetes		
In-target glycaemic control	0.7 (0.5, 1.0)	0.08
Large for gestational age	**1.9 (1.3, 2.9)**	**0.002**
Preterm delivery	**5.4 (3.9, 7.5)**	**< 0.0001**
Male sex	1.3 (1.0, 1.8)	0.07

Comparisons that are boldface type indicate statistically significant differences.

similar definition [22,23]. Given the period of the present cohort study, it is unlikely that this represents a shift towards treatment with dextrose gel rather than intravenous dextrose that has occurred more recently [24]. There were many significant differences between various intrapartum glycaemic control measures in women with gestational diabetes, including our primary exposure variable in-target glucose control. This significant difference was no longer apparent after adjustment for neonatal factors. Even when considering the unadjusted analyses alone it is difficult to determine whether the significant differences between intrapartum control in mothers of neonates with and without hypoglycaemia are clinically meaningful. In the present cohort, only 7% of women with gestational diabetes had an actionable glucose level and only 1% received intravenous insulin. The population-attributable fraction, defined as the proportion of all cases of neonatal hypoglycaemia that can be attributed to out-of-target intrapartum glycaemic control in the unadjusted analysis, is only 10% for women with gestational diabetes. Additionally, the risk of maternal hypoglycaemia when using intravenous insulin therapy is high and must be considered when weighing the risks and benefits [11,25,26].

The present study has several important strengths. This was the largest cohort study examining the relationship between intrapartum glycaemic control and neonatal hypoglycaemia [27]. Our primary outcome, exposures and analysis plan were published prior to data collection and any additional analyses were labelled as exploratory in nature. Our neonatal outcome data by type of diabetes were consistent with other large cohort studies and clinical trials which support the quality and accuracy of our dataset [2,6,22,23].

We also acknowledge some limitations. There were missing intrapartum glucoses in 14%, 24% and 48% of women with type 1, type 2 and gestational diabetes, respectively. We postulate that the most likely reason for these missing data is that glucose values were not measured and/or recorded on the clinical record. While this is the largest cohort to date, the adjusted odds ratios for in-target glycaemic control and neonatal hypoglycaemia were < 1 (0.4 and 0.7 for women with type 1 and 2 diabetes, respectively) with wide 95% CIs, indicating that the study may have been underpowered to detect a potentially important effect in these groups. Because this was a database study, we may have misclassification of variables including type of diabetes. Another limitation is our lack of a neonatal glucose value in our definition of hypoglycaemia which may have led to the misclassification of neonates as having hypoglycaemia who received intravenous dextrose for another reason. Given the consistency of our numbers with the available literature, this is unlikely to have introduced significant bias [6,22,23]. Additionally, we are unable to comment on the relationship of intra partum glycaemic control to milder forms of neonatal hypoglycaemia not requiring intravenous glucose. Lastly, we did not perform all the possible analyses described in our registered protocol as some were not possible given the available data.

In conclusion, we were unable to identify a significant association between in-target glycaemic control and neonatal hypoglycaemia after adjustment for neonatal factors in this large retrospective cohort study. Neonatal hypoglycaemia was significantly associated with risk factors, such as large-for-gestational-age infant and glycaemic control, that are present prior to the intrapartum period. Given the high risk of maternal hypoglycaemia and the resources required for intravenous insulin therapy, future randomized controlled trials should consider whether more relaxed intrapartum glycaemic targets may be safer in women with diabetes in pregnancy.

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Competing interests

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Supporting Information

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

Table S1. Summary of the data source for included variables.
Table S2. Differences between women with and without intrapartum glycaemic control data.
Table S3. Results of univariate logistic regression for neonatal hypoglycaemia.