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Intrapartum glycemic control and neonatal hypoglycemia in pregnancies complicated by diabetes

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Intrapartum glycemic control and neonatal hypoglycemia in pregnancies complicated by diabetes

by

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A THESIS

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Abstract

Neonatal hypoglycemia is common following pregnancies complicated by diabetes. Current dogma suggests that tight intrapartum glycemic control decreases the risk of neonatal hypoglycemia by avoiding an acute rise in fetal insulin prior to delivery. This thesis reports on two studies that bring to question the association between intrapartum glycemic control and the risk of neonatal hypoglycemia. The first is a systematic review that highlights the paucity of high quality evidence confirming an association between intrapartum glycemic control and neonatal hypoglycemia. The second is the largest cohort to date examining this relationship. It found that after adjustment for important neonatal confounders, in-target intrapartum glycemic control was not significantly associated with neonatal hypoglycemia. When taken as whole, these studies question current guidelines recommending tight intrapartum glycemic control and call for a randomized controlled trial of tight versus more relaxed glycemic targets during the labour and delivery period.

Preface

This manuscript-based thesis centres around two manuscripts. For both manuscripts below, Dr. Yamamoto contributed to the conception and design of the work. She was also responsible for much of the data cleaning and merging, the data analysis, interpretation of the data and the initial drafts of the manuscripts. This work was guided by all committee members (Drs. Stephen Wood, Lois Donovan and Khorshid Mohammad) and co-authors (Dr. Jamie Benham). All committee members and authors contributed to parts of study design, interpretation of the data, in addition to critical revision of the manuscript and final approval. All consented to inclusion of the manuscripts in this thesis. Where applicable, copyright permission has been obtained from the publisher (Appendix). Ethics approval was obtained from the Conjoint Health Research Ethics Board at the University of Calgary (REB16-2093) for the original work presented in this thesis.

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Yamamoto JM, Mohammad K, Donovan LE, Wood S. Neonatal hypoglycemia and intrapartum glycemic control in pregnancies complicated by Type 1, Type 2 and gestational diabetes. *Prepared for submission*

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I would like to thank my thesis supervisor Dr. Stephen Wood for his guidance, support, criticism, and patience over the last few years. As well, I would like to thank my thesis committee members for sharing their expertise, time, and patience. With your guidance, you have made me a better clinician and researcher.

I would like to thank Susan Crawford for her help with large task of data cleaning and merging. We are grateful to the Stewart Diabetes Fund and the Cal Wenzel Family Foundation for funding this project. Last, but certainly not least, I thank my family and friends for their love and support throughout this journey.

Dedication

I dedicate this thesis to my mentor Dr. Lois Donovan to whom I owe so much of my success. Over the years you have been my teacher, my advocate, my confidant, and my friend. You inspire me to be better every day. For all this and more, I thank you.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
BMI	Body Mass Index
CI	Confidence Interval
CGM	Continuous Glucose Monitoring
GDM	Gestational Diabetes Mellitus
HbA1c	Hemoglobin A1c
IDD	Insulin Dependent Diabetes
IQR	Interquartile Range
JB	Jamie Benham
JY	Jennifer Yamamoto
KM	Khorshid Mohammad
LD	Lois Donovan
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
SD	Standard Deviation
SW	Stephen Wood
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
UK	United Kingdom
US	United States of America

Epigraph

The greater the ignorance the greater the dogmatism.

— Sir William Osler

Chapter One: **Introduction**

1.1 Diabetes in Pregnancy

Hyperglycemia in pregnancy is common and affects up to 17% of pregnancies worldwide (1). Its incidence varies widely depending on the definitions used and the risk factors of a given population. Most hyperglycemia in pregnancy (~85%) is gestational diabetes and the remainder is pre-existing diabetes (Figure 1.1) (1). In Alberta, diabetes is diagnosed in at least 6% of pregnancies (2).

Gestational diabetes is typically screened for at 24-28 weeks gestation and is most often managed with lifestyle therapy alone (3). About a third of women with gestational diabetes require pharmacotherapy, generally insulin and/or metformin, in addition to recommended lifestyle changes (3). Pre-existing diabetes is most commonly Type 1 or Type 2 diabetes diagnosed before pregnancy and less commonly other forms of diabetes such as maturity onset diabetes of the young. Type 1 diabetes is an autoimmune condition characterized by insulin-dependence. Both in and outside of pregnancy, persons with Type 1 diabetes require insulin as a life-sustaining therapy. While the development of Type 2 diabetes is multifactorial, it is primarily characterized by insulin-resistance. In pregnancy, most women with Type 2 diabetes generally require insulin.

1.2 Complications Associated with Diabetes in Pregnancy

Unfortunately, diabetes in pregnancy continues to be associated with an increased risk of both obstetric and neonatal complications (4-7). In women with pre-existing diabetes, up to 1 in 2 pregnancies will have a common complication such as large for gestational age, preterm delivery, neonatal hypoglycemia, or neonatal intensive care unit admission (4, 7, 8). As well,

these pregnancies have a two to five-fold increased risk of serious adverse neonatal outcomes (congenital anomaly, stillbirth, or neonatal death) (5, 9, 10). Untreated gestational diabetes is associated with increased obstetric and neonatal complications such as preeclampsia, caesarean section, preterm delivery, shoulder dystocia, neonatal intensive care unit admission, and large for gestational age (11, 12). Because gestational diabetes is typically characterized by hyperglycemia later in pregnancy, it is associated with less frequent and generally less severe complications (3).

1.3 Neonatal Hypoglycemia in Pregnancies with Diabetes

The neonate requires several adaptive mechanisms such as glycogen stores, gluconeogenic precursors, hepatic enzymes, and an intact endocrine system to maintain normal glucose levels (13). Classic risk factors for neonatal hypoglycemia generally cause problems in one or many of these aspects important in glucose metabolism. These risk factors include infants of mothers with diabetes as well as large for gestational age, small for gestational age and preterm infants (14, 15). In pregnancies complicated by diabetes, maternal glycemic control, infant size, and treatment may also influence the risk of neonatal hypoglycemia (8, 16, 17).

Neonatal hypoglycemia is common in pregnancies with diabetes (15, 18, 19). The definition of neonatal hypoglycemia remains contentious in the neonatal literature (20). Given the controversy regarding its definition, there is little surprise that there is quite a range of definitions included in studies examining neonatal hypoglycemia in women with diabetes. Definitions use glucoses from <1.7 mmol/L to ≤2.6mmol/L with or without symptoms or whether the neonate required intravenous treatment (15, 20).

While there is much controversy surrounding its definition, neonatal hypoglycemia is well recognized as a potentially serious complication if left undiagnosed and untreated (20). However, even treated neonatal hypoglycemia has been associated with some neurocognitive impairments into childhood (21). Neonatal hypoglycemia requires careful monitoring and may require admission to the neonatal intensive care unit and treatment with intravenous dextrose. Neonatal hypoglycemia is one of the leading causes of admission to neonatal intensive care units with a mean cost of >£3800 ($6500) per neonate (22). This is costly not only in terms of healthcare resources but also may incur other important costs such as maternal infant separation and effects on breastfeeding initiation.

1.4 Maternal Intrapartum Glycemic Control and Neonatal Hypoglycemia – The Current Dogma

Maternal hyperglycemia in labour is thought to increase the risk of neonatal hypoglycemia by triggering an acute rise in fetal insulin (23). Following delivery, the neonate's insulin remains high but they no longer have excess maternal glucose delivery through the placenta and therefore their glucose levels fall (Figure 1.2).

Current dogma suggests tight glucose control during labour is thought to decrease the risk of neonatal hypoglycemia by preventing this acute rise in fetal insulin in response to maternal hyperglycemia (23). Tight glycemic control is generally achieved through use of insulin therapy, administered subcutaneously or intravenously (3). This requires additional close monitoring of maternal glucose (generally capillary blood glucose testing every 1 hour) and a frequent

assessment examining for signs and symptoms of hypoglycemia throughout labour, delivery and immediately postpartum. This is due to the high risk of maternal hypoglycemia associated with insulin therapy at time of delivery with up to 56% of women experiencing at least one episode during the labour and delivery period (24).

The literature regarding the importance of glucose control during labour remains inconsistent (23, 25-28). A review done by Ryan and Al-Agha in 2014 found 19 studies that sought to examine the relationship between maternal glycemic control and neonatal hypoglycemia (23). Of the 19 studies, 10 found a significant inverse relationship between intrapartum glycemic control and neonatal hypoglycemia and 9 did not demonstrate this effect. There may be many reasons for the heterogeneity of the results in these studies. Firstly, only 10 of those studies were published in the last 20 years. This is important since the management of diabetes both during and outside of pregnancy has changed dramatically. In the last 20 years, we have seen the introduction of new insulins and diabetes technologies as well as the publication of important landmark trials in the treatment of diabetes (6, 18, 29-31). The introduction of these tools may have contributed to better glycemic control during pregnancy. This may have influenced the risk of neonatal hypoglycemia as the literature suggests the risk of neonatal hypoglycemia is affected by glycemic control in the third trimester (8, 16, 32). Secondly, given the controversy regarding the definition of neonatal hypoglycemia, there is little surprise that there is quite a range of definitions included in this literature. These studies use glucoses from <1.7 mmol/L to <2.6 mmol/L with or without symptoms or whether the neonatal required intravenous treatment (23). Furthermore, the definition of in-target glycemic control also has a variety of definitions (23). Many of the studies use the glucose closest to delivery as within or outside of target; this may not

accurately represent the range of glucoses a woman may have over the course of her labour and delivery and therefore effect the consistency of results. Thirdly, the type of diabetes (Type 1, Type 2 or gestational diabetes) may influence the importance of intrapartum glycemic control on risk of neonatal hypoglycemia. For instance, in studies primarily in women with gestational diabetes, most have not found an inverse relationship between intrapartum glycemic control and neonatal hypoglycemia (25-28). Lastly, many of these studies had small numbers, incomplete adjustment, and other methodological shortcomings that may have affected the internal validity. When this thesis was initially proposed, no rigorous systematic reviews had been performed examining the association between intrapartum glycemic control and neonatal hypoglycemia.

Intensive intrapartum glucose control is the standard of care despite these conflicting data and the high risk of maternal hypoglycemia and increased resource utilization associated with intravenous insulin therapy. In fact, recommendations of the Diabetes Canada Clinical Practice Guidelines and other international guidelines for intrapartum glucose control (between 4.0 and 7.0 mmol/L) are based on consensus rather than high quality evidence (3, 33).

1.5 Thesis Outline

Neonatal hypoglycemia remains a common and potentially serious adverse outcome following pregnancies with diabetes. While current dogma suggests tight intrapartum control is essential to decrease the risk of neonatal hypoglycemia, it is unclear if this is evidence based. Through the work contained in this thesis, we set out to better understand the relationship between neonatal hypoglycemia and intrapartum glycemic control.

In chapter 2, we describe the results of our systematic review of the literature examining this relationship (34). This includes a compilation and assessment of the available studies in women with Type 1, Type 2, and gestational diabetes.

In chapter 3, we describe the results of our retrospective cohort study examining the relationship between neonatal hypoglycemia and intrapartum glycemic control in women with Type 1, Type 2 and gestational diabetes. For this study, we created a new dataset through the linkage of various databases. Ours is the largest cohort to date examining the association of intrapartum glycemic control with neonatal hypoglycemia.

Finally, in chapter 4 we summarize the findings of this thesis. We conclude with the implications on health policy and future directions for research.

1.6 Figures

Figure 1.1: Types of Diabetes in Pregnancy

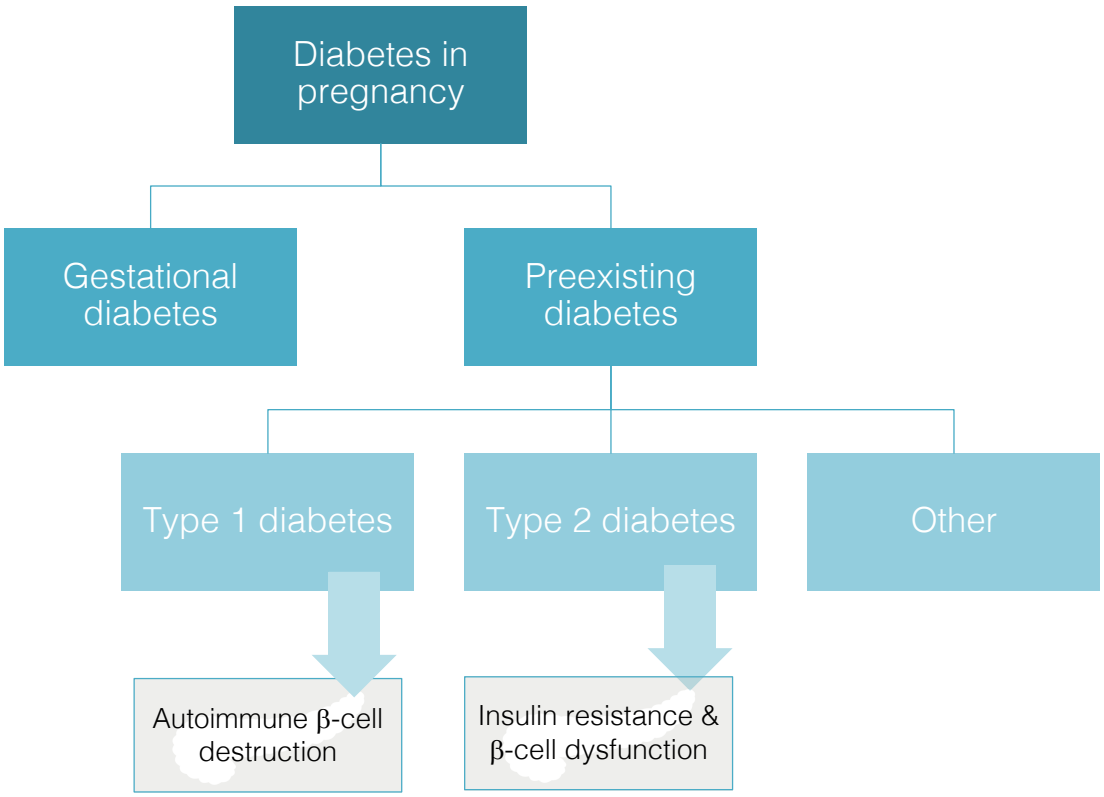
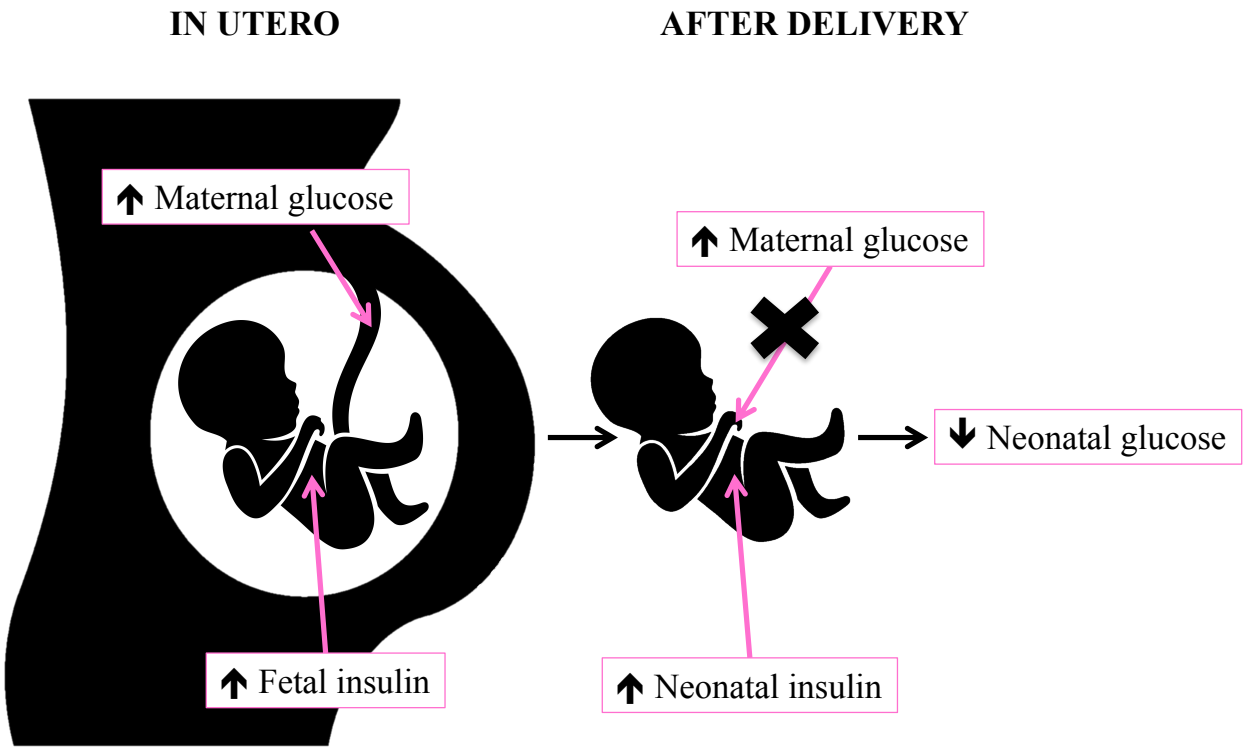


Figure 1.2: Diagram of Theoretical Relationship between Maternal Intrapartum Hyperglycemia and Neonatal Hypoglycemia



Chapter Two: **Intrapartum glycemic control and neonatal hypoglycemia in pregnancies complicated by diabetes: a systematic review**

This chapter is published as:

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Diabet Med. 2018 Feb;35(2):173-183. doi: 10.1111/dme.13546. (34)

2.1 Abstract

Aims: To examine whether, in neonates of mothers with Type 1, Type 2 and gestational diabetes, in-target intrapartum glycemic control was associated with a lower risk of neonatal hypoglycemia compared with out-of-target glycemic control.

Methods: We searched PubMed and EMBASE for all available publications, regardless of year, based on a published protocol (PROSPERO CRD42016052439). Studies were excluded if they did not report original data or were animal studies. Data were extracted from published reports in duplicate using a pre-specified data extraction form. The main outcome of interest was the association between in-target intrapartum glycemic control and neonatal hypoglycemia.

Results: We screened 2846 records for potential study inclusion; 23 studies, including approximately 2835 women with diabetes, were included in the systematic review. Only two of those studies specifically examined in-target vs out-of- target intrapartum glycemic control. Of the studies included, six showed a relationship between intrapartum glucose and neonatal hypoglycemia, five others showed a relationship in at least one of the analyses performed and 12 did not find a significant relationship. Only one study was identified as having a low risk of bias.

Conclusions: There is a paucity of high-quality data supporting the association of glucose during labour and delivery with neonatal hypoglycemia in pregnancies complicated by diabetes. Further studies are required to examine the impact of tight glycemic targets in labour.

2.2 Introduction

Neonatal hypoglycemia is a common and potentially serious outcome in pregnancies complicated by diabetes (24, 35). The spectrum of neonatal hypoglycemia is wide and ranges from mild and easily treated hypoglycemia to severe and prolonged hypoglycemia, requiring admission to the neonatal intensive care unit. In women with diabetes, maternal hyperglycemia has been shown to trigger an acute rise in fetal insulin (23). Tight glucose control during labour aims to prevent this rise in fetal insulin in response to maternal hyperglycemia, with the goal of decreasing the risk of neonatal hypoglycemia (23, 36). During labour and delivery, glycemic control is often achieved or maintained by insulin therapy, administered subcutaneously or intravenously. This requires additional close monitoring throughout labour because insulin therapy at time of delivery is associated with maternal hypoglycemia in up to 56% of women with Type 1 diabetes (24).

The literature regarding the importance of glucose control during labour is inconsistent (23, 25-28). A review carried out by Ryan and Al-Agha (23) in 2014 found 19 studies that sought to examine the relationship between maternal glycemic control and neonatal hypoglycemia. Of the 19 studies identified, 10 found a significant inverse relationship between intrapartum maternal glucose and offspring glucose levels and nine did not demonstrate a significant effect. That review was limited in that it was not clear if rigorous systematic methods were used and there was no assessment of the quality of studies it included.

Currently, intensive intrapartum glucose control is the standard of care despite these conflicting data. Both the Diabetes Canada 2013 Clinical Practice Guidelines and the National Institute for

Health and Care Excellence (NICE) guidelines for diabetes in pregnancy recommend intrapartum glucose control (4.0–7.0 mmol/L) (37, 38); however, no rigorous systematic reviews have been performed on this subject.

To address this gap, we performed a systematic review to examine whether, in neonates of mothers with Type 1, Type 2 or gestational diabetes, in-target intrapartum glycemic control was associated with a lower risk of neonatal hypoglycemia compared with out-of-target glycemic control.

2.3 Methods

We performed a systematic review based on a pre-published protocol (PROSPERO CRD42016052439) and reported it in accordance with specifications recommended by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (39).

2.3.1 Search strategy and selection criteria

PubMed and EMBASE were searched in duplicate using the strategy outlined in Supplementary Table 2.1 for all available time periods after consultation with a medical librarian. The references of all included articles were also hand-searched by both reviewers to identify potential additional articles for inclusion. Local experts in the field were consulted for additional studies.

An initial screen of titles and abstracts was performed independently by two reviewers (JY and JB) to identify articles that required further review. Articles were included if they reported on neonatal hypoglycemia after pregnancies complicated by diabetes, analyzed by intrapartum

glycemic control. Studies were excluded from the systematic review if they did not report on original data or were animal studies. Studies were not excluded based on language, study type or publication status.

As per our pre-specified protocol, all types of maternal diabetes were included and no restrictions on the definition of diabetes were imposed. Either of the following definitions of in-target glycemic control were included: a single glucose value closest to and prior to delivery or a given proportion of glucose values during labour and delivery that was/were considered in-target as specified by the authors. Any definition of neonatal hypoglycemia was accepted if it included at least one of the following: a specific glucose cut-off level; neonate requiring treatment with glucose administered intravenously/orally; or symptoms of hypoglycemia.

Based on the above criteria, two reviewers determined study eligibility by screening all titles and abstracts from retrieved studies, as well as full papers when necessary. Kappa statistics for both the title and abstracts as well as the full-text review were calculated to assess inter-rater agreement.

2.3.2 Data analysis

Two reviewers (JB and JY) independently extracted data using a pre-specified extraction form. Discrepancies between reviewers were resolved by consensus with discussion between the two reviewers. Extracted data elements included: general information, eligibility criteria, study characteristics (including design, country, type of diabetes, sample size), definition of diabetes, intrapartum glucose target, definition of neonatal hypoglycemia, and definition of maternal

hypoglycemia, as well as details of the results including percent neonatal hypoglycemia, percent of maternal hypoglycemia, effect size of intrapartum glycemic control, percentage of large-for-gestational-age neonates, percentage of preterm deliveries, and mode of delivery. When available, both unadjusted and adjusted odds ratios with 95% CIs were extracted from the studies included. Data were managed using Microsoft Excel (version 14.4.8, Microsoft Corporation).

Each reviewer assessed study quality independently based on the following domains: participation; attrition; prognostic factor measurement; outcome measurement; statistical analysis; and confounding measure and account (Supplementary Table 2.2) (40). Studies were scored as having a high risk, a low risk or an unclear risk of bias based on each of these domains. Only studies that scored as low-risk on each of the six domains were classified as having a low risk of bias.

2.4 Results

We screened 2846 records for potential study inclusion. After title and abstract review, full-text review was performed on 86 articles. Of those, 23 studies were included in the systematic review (Fig. 2.1). Only two of those studies specifically examined in-target vs out-of-target intrapartum glycemic control (25, 41). The kappa statistic for inter-rater agreement for inclusion after the title and abstract review was 0.30 (95% CI 0.23,0.37), and for the full-text review it was 0.77 (95% CI 0.56, 0.99).

2.4.1 Study characteristics

Details of the study characteristics are found in Table 2.1 (24, 25, 27, 28, 41-59). All 23 studies identified were cohort studies. While some cohorts were based on randomized trials, we did not identify any trials randomizing intrapartum glycemic targets in women with diabetes that met our inclusion criteria. The 23 studies included ~2835 women with diabetes. We are unable to report an exact number of participants included because not all studies reported on the number of mothers. Of the women included, 867 had Type 1 diabetes, 244 had Type 2 diabetes, 1428 had gestational diabetes, 235 had 'insulin-dependent' diabetes and 61 were unclear. Of the studies included, seven comprised only women with Type 1 diabetes and four comprised only women with gestational diabetes. The remainder of the studies included a combination of women with Type 1 diabetes, Type 2 diabetes, gestational diabetes and/or insulin- dependent diabetes. All studies were performed in North America, Europe, New Zealand, or Australia. Studies ranged in size from 15 to 733 women.

The intrapartum glucose targets are shown in Table 2.1. The highest upper limit was 8 mmol/L and the lowest lower limit was 2.8 mmol/L. The definitions of neonatal hypoglycemia were variable and ranged from glucose levels <1.5 mmol/L to <2.6 mmol/L. Most definitions were based on neonatal glucose alone, but some included symptoms, admission to the neonatal intensive care unit or treatment with intravenous glucose.

2.4.2 Intrapartum glucose and neonatal hypoglycemia

Of the studies included, six showed a relationship between intrapartum glucose and neonatal hypoglycemia, five other studies found a relationship in at least one of the analyses performed

and 12 studies did not show a statistically significant difference (Table 2.2) (24, 25, 27, 28, 41-59). Because of the small number of studies identified, as well as the heterogeneity of study populations, definitions and analysis, the meta-analysis specified in the published protocol was not performed.

2.4.3 Studies that found a relationship

In six studies a relationship between intrapartum glucose and neonatal hypoglycemia was observed (Table 2.2) (42-46, 59). The most recently published of these was a study in 2002 by Taylor et al. (42), who observed a significant correlation between mean maternal blood glucose in labour and neonatal blood glucose ($r=-0.33$, $P<0.001$) in 107 women with Type 1 diabetes.

2.4.4 Studies with mixed results

In five of the included studies, authors found a relationship between neonatal hypoglycemia and intrapartum maternal glucose in some analyses, but not others (Table 2.2) (24, 25, 47-49). Interestingly, two of these studies used continuous glucose monitoring during labour and delivery (47, 48). Cordua et al. (47) found that women who had infants with hypoglycemia spent a larger percentage of time with glucose levels >7 mmol/L according to the continuous glucose monitor than those who did not; however, there was no difference when the analyses were performed on the self-monitored glucose values (Table 2.2). Stenninger et al. (48) found that higher glucose concentrations obtained by continuous glucose monitors were associated with the need for intravenous glucose at delivery for the neonate; however, they did not show a statistically significant difference between mean maternal glucose and infant glucose

concentrations (Table 2.2). These were the only two studies identified that used continuous glucose monitoring (47, 48).

2.4.5 Studies that did not find a relationship

Twelve of the included studies did not find a statistically significant relationship between intrapartum glucose level and neonatal hypoglycemia (Table 2.2) (27, 28, 41, 50-58). These studies included all types of diabetes. The largest of these studies included 733 women with gestational diabetes (50). Using logistic regression, the authors did not find any significant associations between tertiles of glucose control in labour and neonatal hypoglycemia (odds ratio not reported) (50). The largest cohort of women with Type 1 diabetes included 229 pregnancies (in 174 women) and found no correlation between neonatal hypoglycemia at 3 h of life and maternal glycemia during labour ($r=0.12$, $P=0.29$); however, they treated all neonates prophylactically with glucagon and triglycerides (53). The second largest cohort of women with Type 1 diabetes studied 161 women and found no statistically significant association between neonatal hypoglycemia and in-target glycemic control, defined as 100% of the time within 4.0 to 6.0 mmol/L, vs out-of-target, defined as 0% of the time in-target, (unadjusted odds ratio 0.41 [95% CI 0.16, 1.05], adjusted odds ratio 0.47 [CI not reported]; $P=0.15$) (41). None of the included studies examined only women with Type 2 diabetes. Two of these studies had a potential overlap in women (28, 52). All three studies in which exclusion of preterm deliveries was documented did not show an association between intrapartum control and neonatal hypoglycemia (27, 48, 51).

2.4.6 Other participant characteristics in included studies

The percentage of participants with preterm delivery ranged from 5.3 to 29.9% and was not reported in 12 of the 23 studies (Table 2.3) (24, 25, 27, 28, 41-59). Three studies excluded preterm deliveries (27, 48, 51). The percentage of infants with macrosomia or who were large for gestational age ranged from 9.4% to 55.6%, and was not reported in 13 of the 23 studies. The percentage of caesarean sections ranged from 12.9% to 75.4%, and six studies did not report on mode of delivery or restricted their analysis to vaginal deliveries only (Table 2.3). The percent of mothers experiencing maternal hypoglycemia during labour and delivery was quite wide (0 to 56.0%), with seven studies not reporting on maternal hypoglycemia.

2.4.7 Study quality

Study quality assessment is shown in Table 2.4 (24, 25, 27, 28, 41-59). Only one of the 23 studies included was thought to have a low risk of bias in all six domains assessed (41). The more contemporary studies seemed to have a lower risk of bias than the older studies. Confounding measurement and account was the most frequent quality assessment criterion to be assessed as high or unclear, with only one study clearly adjusting for important confounders (41). While no statistical test can be used to assess differences in results based on risk of bias, in the present study, we note that none of the six studies that showed a significant relationship between intrapartum glucose levels and neonatal hypoglycemia clearly adjusted for known confounders.

2.5 Discussion

In this systematic review, we show that the relationship between intrapartum glucose and neonatal hypoglycemia is inconsistent across studies. Furthermore, we highlight the

heterogeneity of the studies in terms of participants included, intrapartum glucose targets, definitions of neonatal hypoglycemia, adjustment for confounders and analyses used.

Adjustment for known confounders was either not present or unclear in the vast majority of the studies. This could have contributed to the heterogeneity of study conclusions. There are many other risk factors for neonatal hypoglycemia, such as small-for-gestational-age or large-for-gestational-age neonates, preterm delivery, maternal BMI and third trimester glycemic control that have confounded the relationship between maternal and neonatal glucose (8, 15, 60). None of the six studies that consistently found a relationship between neonatal hypoglycemia and intrapartum glucose included an analysis that adjusted for potential confounding factors. Additionally, none of the three studies that excluded preterm delivery, a known risk factor for neonatal hypoglycemia, found an association between intrapartum maternal glucose and neonatal hypoglycemia.

Multiple methods of analysis were used to assess the relationship between intrapartum glucose and neonatal hypoglycemia, such as logistic regression, correlation coefficients, t-tests, chi-squared tests and some non-parametric tests. Most of these tests do not permit confounding adjustment. While an inverse correlation between maternal and neonatal glucose or a difference in mean maternal glucose in mothers of neonates with and without hypoglycemia is interesting and hypothesis-generating, it is not clear whether this translates well into clinical practice. It may be more clinically relevant to study whether ‘in-target’ glucose vs ‘out-of-target’ glucose is associated with neonatal hypoglycemia as these measures are clinically oriented and potentially achievable. Only two of the studies we examined looked at the association between mothers with

in-target intrapartum glucose levels vs those without (25, 41). These studies had discordant results. Drever et al. (41) did not find a statistically significant association after adjustment for gestational age, first and third trimester HbA1c, pre-pregnancy weight and pre-eclampsia. Whereas Balsells et al. (25) performed 12 models, three of which found a statistically significant relationship. They did not include third trimester HbA1c, small-for-gestational-age neonate, preterm birth or insulin treatment in any of these three models. Lastly, many of these studies performed multiple analyses to examine an association which were not clearly pre-specified. This may have increased the risk of type 1 error.

Changes in diabetes care over time may also have contributed to the heterogeneity of the present study findings. Our review included studies with publication dates ranging from 1978 to 2016. Over these 38 years, diabetes care has changed substantially. We have seen the introduction of short- and long-acting insulin analogues, insulin pens, improved glucose testing devices, increasing use of other technologies, such as the insulin pump and continuous glucose monitors, the publication of important landmark trials in gestational diabetes, and tighter glycemic targets throughout pregnancy (11, 29-31). Glycemic control during pregnancy has been associated with neonatal hypoglycemia in previous studies; therefore, improved diabetes management and more aggressive treatment targets may have played a role in the divergent results of the various studies (11, 16). It is noteworthy that the most recent study to demonstrate a relationship between intrapartum glucose and neonatal hypoglycemia was published in 2002, which raises doubts about the relative impact of glycemic control during pregnancy vs glycemic control intrapartum. Perhaps intrapartum glycemic control is less important when glucose control during pregnancy is

optimized.

The most important strength of the present systematic review is its use of rigorous methodology throughout. The study also has some limitations. Firstly, while we can speculate on possible reasons for the heterogeneity of study results, we cannot be certain that these have caused the discordance in the literature. Secondly, many of the studies were small and may have lacked adequate power to detect a clinically significant difference, and alternatively, a small-study effect may have led to publication bias, with small positive studies being more likely to be published than small negative studies. Lastly, because of the heterogeneity of the current literature, we were unable to perform a meta-analysis of included studies.

In conclusion, the present systematic review highlights the paucity of high-quality evidence supporting the association of glycemic control during labour and delivery and neonatal hypoglycemia in pregnancies complicated by Type 1 diabetes, Type 2 diabetes and gestational diabetes. While we recognize that, in theory, there is a pathophysiological mechanism suggesting that hyperglycemia during labour and delivery may increase the risk of neonatal hypoglycemia, given the lack of high-quality studies and discordant results of the available studies, we cannot draw conclusions about the need or lack of need for tight glycemic control based on the available evidence. Given the risk of maternal hypoglycemia, and potential increased need for healthcare resources, large high-quality studies are needed to further examine if there is indeed a role for tight glycemic targets in labour and delivery, such as those recommended in the current guidelines, or if a more relaxed approach is safer, while yielding similar outcomes.

2.6 Acknowledgements

We would like to thank Ms. Diane Lorenzetti (Department of Community Health Sciences, University of Calgary, Calgary, Canada) for her advice with our search strategy as well as Dr. Xin Feng for his help with translating articles in Chinese.

2.7 Contributors

JY, JB, LD, KM and SW conceived and designed the study. JY and JB performed the search, data extraction and data analysis. JY wrote the manuscript. JY, JB, LD, KM and SW all participated in the critical revision of the manuscript for important intellectual content and approved the final version. JY is the guarantor of this work, had full access to all the study data and takes responsibility for the integrity of the data.

2.8 Tables and Figures

Table 2.1: Study Characteristics and Definitions

Study (year)	Country	Type of diabetes	n	Study design	Intrapartum glucose target (mmol/L)	Definition of neonatal hypoglycemia (mmol/L)	Definition of maternal hypoglycemia (mmol/L)	Definition of GDM
Drever et al (2016) (41)	Canada	T1D	161	Retrospective cohort	4-6	<2.6	<3.5	Not applicable
Farrant et al (2017) (50)	New Zealand and Australia	GDM	733	Prospective cohort	<7.0	<2.6 on 2^{+} occasions; <1.6 severe	Not reported	Australian Diabetes in Pregnancy Society
Sargent et al (2015) (51)	USA	T1D	95	Retrospective cohort	3.9-6.7	<2.5 in 1st 24 hours	Not reported	Not applicable
Cordua et al (2013) (47)	Denmark	T1D	27 included in analysis	Prospective cohort	4-7	<2.5 2-hour plasma glucose	<3.0	Not applicable
Flores-le Roux et al (2012) (52)	Spain	GDM	190 infants	Prospective cohort	3.8-7.2	<2.5 (divided by mild, moderate and severe)	<3.3	3rd International Workshop
Flores-Le Roux et al (2010) (28)	Spain	GDM	129	Prospective cohort	≤7.2	<2.2 within the first 24 hours of life	<3.0	3rd International Workshop
Barrett et al (2009) (27)	Australia	T1D T2D GDM	18 5 114 137 total	Retrospective cohort	4-8	<2.6	<4.0	Not reported
Lepercq et al (2008) (53)	France	T1D	174 (229 pregnancies)	Prospective cohort	3.4-7.8	<2 at 3 hours despite preventative treatment	≤3.3	Not applicable
Stenninger et al (2008) (48)	Sweden	T1D T2D GDM	15	Prospective cohort	<7.0	<2.2	Not reported	Not reported
Kline et al (2007) (24)	Canada	T1D T2D	59 41 100 total	Retrospective cohort	4-6.5	<2.2 (or admission to neonatal intensive care for hypoglycemia or treatment with intravenous glucose)	<4.0	Not applicable
Taylor et al (2002) (42)	UK	T1D	107	Retrospective cohort	4-8	<2.5	<3.0	Not applicable
Agrawal et a (2000) (54)	Australia	T1D T2D GDM	5 (T1D & T2D) 33 38 total;	Prospective cohort	4-8	<2.0	<4.0	75g glucose non-fasting load; if 1 hour glucose >8mmol/L patients had fasting 75g oral

								glucose tolerance test; GDM if fasting >5mmol/L or 2h >8mmol/L
Balsells et al (2000) (25)	Spain	GDM	85	Prospective cohort	2.8-6.9	2 or more <1.7 for term, <1.1 for preterm or small-for-gestational-age	<2.8	3rd and 4th International Workshops
Carron Brown et al (1999) (49)	UK	T1DM	80 (40 infants had glucose measured)	Retrospective cohort	4-7	<2.2	<3.0	Not applicable
Curet et al (1997) (43)	USA	T1D T2D	77 156 233 total	Prospective cohort	3.3-5.0	<2.2 or signs of hypoglycemia	Not reported	Not applicable
Njenga et al (1992) (55)	UK	T1D	37 (40 pregnancies)	Retrospective cohort	3-6.0	<2.2	Not reported	Not applicable
Stenninger et al (1991) (56)	Sweden	IDD GDM	10 26 36 total	Retrospective cohort	Not reported	<1.5	Not reported	Not reported
Lean et al (1990) (44)	UK	"Insulin treated"	25	Retrospective cohort	3-8	<2.0	Unclear	Not reported
Miodovnik et al (1987) (45)	USA	IDD	100 (122 pregnancies)	Prospective cohort	3.9-5.6	<1.7	Not reported	Not reported
Plehwe et al (1984) (46)	Australia	T1D T2D GDM	72 9 151 232 total	Retrospective cohort	Not reported	<2.2	Not reported	National Diabetes Data Group
Haigh et al (1982) (57)	Canada	IDD	50	Retrospective cohort	Not reported	<1.7	<3.3	Not reported
Yeast et al (1978) (58)	USA	Unclear	16	Retrospective cohort	3.9-7.2	<1.7	Not reported	Not reported
Soler et al. (1978) (59)	UK	IDD	75	Prospective cohort	Not reported	<1.7	<2.2	N/A

T1D, Type 1 diabetes; GDM, Gestational diabetes mellitus; T1D, Type 2 diabetes; IDD, “Insulin Dependent Diabetes”

Table 2.2: Study Results Analyzing Relationship Between Intrapartum Glucose and Neonatal Hypoglycemia

Study (year)	Analyses Performed	Results	Adjustment for confounders	Relationship: Yes/No
Drever et al (2016) (41)	Unadjusted and adjusted OR analyzing the association between a higher proportion of time spent in target glucose range and neonatal hypoglycemia	Unadjusted OR 0.41 (95% CI 0.16, 1.05) Adjusted OR 0.47, p=0.15	Yes (Both adjusted and unadjusted)	No
Farrant et al (2017) (50)	Tertiles of glucose control and neonatal hypoglycemia	No significant association (OR not reported)	Unclear	No
Sargent et al (2015) (51)	Mean intrapartum glucose of mothers of infants with and without neonatal hypoglycemia Last glucose before delivery of mothers of infants with and without neonatal hypoglycemia	No difference (6.1mmol/L (IQR 5.6, 6.9) and 6.3mmol/L (IQR 5.7, 7.3) respectively, p=0.207) No difference (5.8mmol/L (IQR 5.3, 6.7) and 6.7mmol/L (IQR 5.5, 7.8) respectively, p= 0.073)	No	No
Cordua et al (2013) (47)	% of time >7.0mmol/L by continuous glucose monitor in mothers of infants with neonatal hypoglycemia versus those without % of self-monitored glucoses >7.0mmol/L in mothers of infants with neonatal hypoglycemia versus those without Linear regression of median maternal self-monitored plasma glucose and 2-hour plasma glucose of infant	17% vs 4% respectively (p=0.02) No difference (26% vs 9% respectively, p=0.17) No relationship (r=-0.39, p=0.45)	No	Yes and No
Flores-le Roux et al (2012) (52)	Mean glucose in mothers of infants with and without neonatal hypoglycemia Delivery glucose in mothers of infants with and without neonatal hypoglycemia	No difference (5.4±1.07mmol/L and 5.5±1.07mmol/L respectively, p=0.740) No difference (5.7±1.18mmol/L and 5.7±1.18mmol/L, p=0.912)	No	No
Flores-Le Roux et al (2010) (28)	Mean maternal glucose during labour Any glucose ≥7.2mmol/L Delivery glucose	No difference (p=0.11) No difference (p=0.95) No difference (p=0.09)	No	No
Barrett et al (2009) (27)	Maternal glucose prior to delivery and first neonatal glucose	No relationship (R square 0.003)	No	No
Lepercq et al (2008) (53)	Neonatal hypoglycemia and maternal glycemia during labour Glucose at delivery	No correlation (r=0.12, p=0.29) No correlation (r=-0.3, p=0.71) Note: (glucagon and medium-chain triglycerides routinely used)	No	No

Stenninger et al (2008) (48)	Association of area under the curve at 0-120 min and need for intravenous glucose Association of mean glucose concentrations in mothers whose infants did require intravenous glucose versus those who did not Mean maternal glucose concentrations before delivery and infant glucose concentration	Association found (p=0.028) Association found (7.5±2.2mmol/L and 5.3±1.5mmol/L respectively, p=0.028) No relationship (p-value not reported)	No	Yes and No
Kline et al (2007) (24)	Neonatal glucose <2.2 mmol/L Admission to neonatal intensive care unit for hypoglycemia Admission to neonatal intensive care unit or received intravenous glucose	Unadjusted OR 3.0 (95% CI 1.2-7.9), p=0.037 Unadjusted OR 2.0 (95% CI 0.88, 4.6), p=0.140 Unadjusted OR 1.71 (95% CI 0.75, 3.9), p=0.280	No	Yes and No
Taylor et al (2002) (42)	Correlation between neonatal glucose and mean maternal glucose in labour Correlation between neonatal glucose and mean maternal glucose in labour when maternal blood glucose within target range	Significant correlation (r=-0.33, p<0.001) No relationship (p-value not reported)	No	Yes
Agrawal et a (2000) (54)	Mean maternal glucose between infants with and without hypoglycemia	No difference (4.93±1.11mmol/L and 4.98±1.07mmol/L, p=0.879)	No	No
Balsells et al (2000) (25)	Mean or highest glucose during labour, mean or highest glucose in last 4 hours Mean or highest glucose in last 2 hours 12 logistic regression models: Maximal glucose in labour Maximal glucose during last 4 hours of labour Mean blood glucose in last 2 hours of labour	No difference No difference (“Non-significant”, p-values not reported) 8 models found no association and 3 models reached significance reported below: OR 18.47, p<0.05 OR 18.51, p<0.05 OR 18.68, p<0.05 (CIs not reported)	Yes and No	Yes and No
Carron Brown et al (1999) (49)	Mean maternal glucose at delivery in mothers of neonates with hypoglycemia versus all other women Correlation between first recorded neonatal glucose and maternal glucose at delivery	7.7+/-3.8mmol/L and 4.9+/-2.8mmol/L respectively (p=0.05) No correlation (r=-0.35; p=0.08)	No	Yes and No

	Correlation of maternal blood glucose on neonatal blood glucose if within target range Blood glucose of infants if maternal blood glucose was >10mmol/L	No correlation (p-value not reported) The infants blood glucose was always low (glucose of 1.3±0.8mmol/L versus 2.5±1.5mmol/L; p<0.02)		
Curet et al (1997) (43)	Intrapartum glucose of mothers of infants with neonatal hypoglycemia versus mothers of infants without	5.9±2.9mmol/L versus 4.5±1.8mmol/L respectively (p<0.05) (Note: the last 125 patients not included in analysis because they were "in-target")	No	Yes
Njenga et al (1992) (55)	Mean maternal glucose at delivery for mothers of neonates with and without hypoglycemia	No difference (4.3 ± 1.4 vs 4.7 ±1.6 respectively; p>0.7)	No	No
Stenninger et al (1991) (56)	Correlation between blood glucose of the mother at delivery and the glucose of the infant	No correlation (p-value not reported)	No	No
Lean et al (1990) (44)	Correlation between neonatal glucose and maternal glucose at delivery was found	An inverse relationship found (r_s=-0.58, p<0.01)	No	Yes
Miodovnik et al (1987) (45)	Correlation between the lowest infant glucose concentration in the first 4 hours of life and the highest maternal glucose within 4 hours before delivery Percentage of infants with neonatal hypoglycemia in mothers with a glucose >5 during the last 4 hours before delivery versus those without	Significant correlation (r=-0.29, p=0.002) 47% versus 14%, (p=0.0003)	No	Yes
Plehwe et al (1984) (46)	Infants of those mothers whose maximum glucose >10mmol/L or mean glucose >8mmol/L or nadir >6mmol/L	All more likely to have documented hypoglycemia (p=0.0007, 0.0204, 0.0132)	No	Yes
Haigh et al (1982) (57)	Correlation between the maternal glucose during labour and the glucose in the newborns	No correlation	No	No
Yeast et al (1978) (58)	Association between glucose in mother and the incidence or severity of neonatal hypoglycemia	No association	No	No
Soler et al. (1978) (59)	Incidence of neonatal hypoglycemia by mean maternal glucose in the following groups <5, 5-7.2 and >7.2mmol/L	Significant difference (p<0.025)	No	Yes

OR: Odds Ratio; IQR: Interquartile range; CI: confidence interval

Table 2.3: Pregnancy Characteristics from Included Studies

Study (year)	n (%) neonatal hypoglycemia	n (%) maternal hypoglycemia	n (%) preterm delivery	n (%) Large-for-gestational-age or macrosomia	n (%) Caesarian section
Drever et al (2016) (41)	60 (39.0)	50 (31.1)	33 (20.6)	33 (20.5)	96 (60)
Farrant et al (2017) (50)	124 (16.9)	Not reported	72 (9.8)	Not reported	273 (37.2)
Sargent et al (2015) (51)	62 (66.0)	Not reported	≥36 weeks only	31 (32.6)	66 (69.5)
Cordua et al (2013) (47)	10 (37.0)	3.5% of glucose values	5 (19.0)	15 (55.6)	7 (25.9)
Flores-le Roux et al (2012) (52)	48 (25.3)	0 (0)	10 (5.3)	30 (15.8)	68 (35.8)
Flores-Le Roux et al (2010) (28)	15 (11.8)	0 (0)	7 (5.4)	12 (9.4)	43 (33.6)
Barrett et al (2009) (27)	34 (24.8)	11 (8.0)	≥37 weeks only	18 (13.1)	74 (54.0)
Lepercq et al (2008) (53)	30 (13.1)	16 (7.0)	25.8%	Not reported	158 (69.0)
Stenninger et al (2008) (48)	9 (60.0)	Not reported	≥37 weeks only	Not reported	0 (0)
Kline et al (2007) (24)	69 (69.0)	56 (56.0)	Not reported	Not reported	49 (49.0)
Taylor et al (2002) (42)	50 (46.7)	13 (12.1)	32 (29.9)	39 (36.4)	53 (49.5)
Agrawal et al (2000) (54)	18 (47.4)	2 (5.3)	Not reported	Not reported	18 (47.4)
Balsells et al (2000) (25)	5 (5.9)	28 (32.9)	Not reported	Not reported	11 (12.9)
Carron Brown et al (1999) (49)	19 (47.5)[a]	18 (22.5)	Not reported	Not reported (43.1)	41 (51.3)
Curet et al (1997) (43)	38 (16.5)	Not reported	Not reported	Not reported	Not reported
Njenga et al (1992) (55)	7 (17.5)	4 (19.0)[b]	Not reported	Not reported	Not reported
Stenninger et al (1991) (56)	14 (38.5)	Not reported	Not reported	10 (27.8)	Not reported
Lean et al (1990) (44)	11 (44.0)	Not reported	Not reported	Not reported	13 (52.0)

Miodovnik et al (1987) [45]	44 (36.0)	Not reported	Not reported	53 (43.4)	92 (75.4)
Plehwe et al (1984) [46]	41 (18.5)[c]	Not reported	Not reported	Not reported	Not reported
Haigh et al (1982) [57]	7 (14.0)	24 (48.0)	Not reported	Not reported	Not reported
Yeast et al (1978) [58]	4 (23.5)[d]	Not reported	Not reported	Not reported	Not reported
Soler et al. (1978) [59]	15 (20.0)	0 (0)	Not reported	Not reported	41 (54.7)

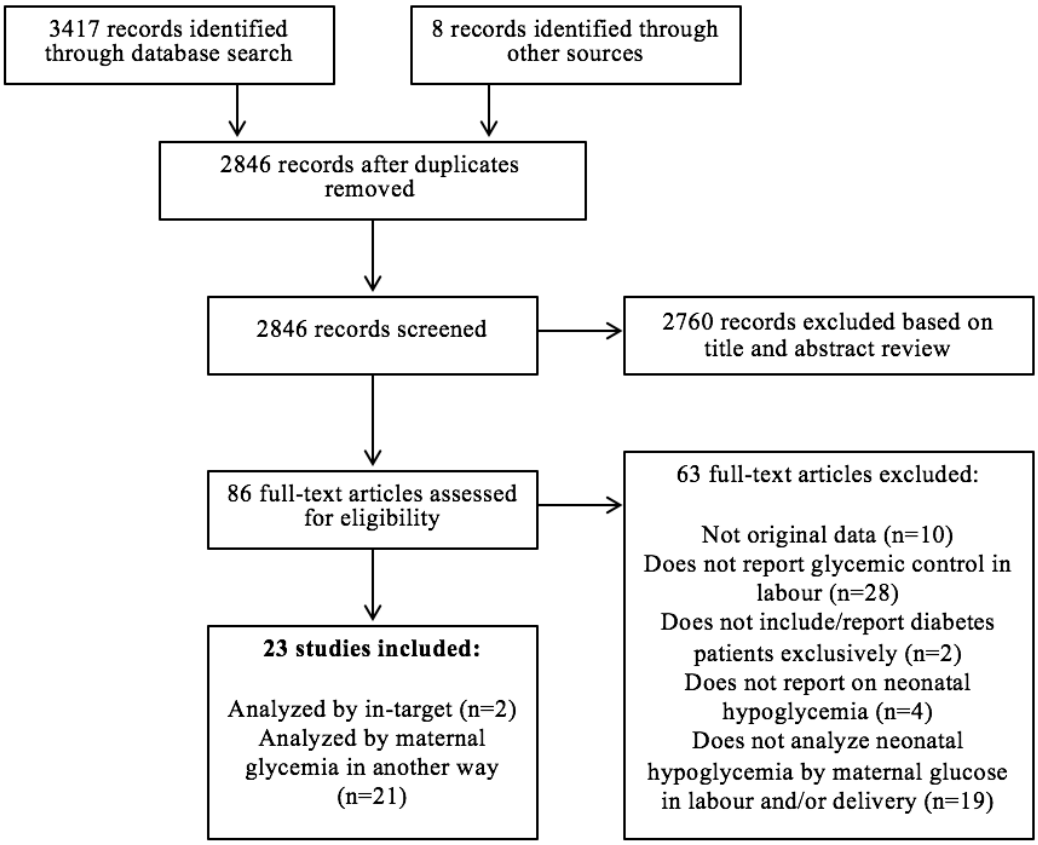
[a]Only measured 40 of 80 infants included; [b]Reported on 21 of the 38 participants included; [c]Based on number of live births; [d]Of the 17 infants included

Table 2.4: Assessment of Study Quality

Risk of bias by potential source	Drever et al. (2016) (41)	Farrant et al. (2017) (50)	Sargent et al. (2015) (51)	Cordua et al. (2013) (47)	Flores-Le Roux et al. (2012) (52)	Flores-Le Roux et al. (2010) (28)	Barrett et al. (2009) (27)	Lepercq et al. (2008) (53)	Stenninger et al. (2008) (48)	Kline et al. (2007) (24)	Taylor et al. (2002) (42)	Agrawal et al (2000) (54)	Balsells et al. (2000) (25)	Carron Brown et al. (1999) (49)	Curet et al. (1997) (43)	Njenga et al. (1992) (55)	Stenninger et a. (1991) (56)	Lean et al. (1990) (44)	Miodovnik et al. (1987) (45)	Plehwe et al (1984) (46)	Haigh et al. (1982) (57)	Yeast et al. (1978) (58)	Soler et al. (1978) (59)
Study participation	L	L	L	L	L	L	L	L	L	L	L	H	?	L	H	H	?	H	H	H	H	H	H
Attrition	L	L	L	L	L	L	L	L	L	L	?	H	?	?	?	?	L	?	?	?	?	?	?
Prognostic factor measurement	L	L	L	L	L	L	L	L	L	L	?	?	H	?	?	L	?	H	H	H	H	?	?
Outcome measurement	L	L	L	L	L	L	L	L	L	L	L	L	L	H	L	L	L	L	L	?	?	L	L
Confounding measurement and account	L	?	?	H	?	H	H	?	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H
Analysis	L	?	L	H	H	H	H	L	H	L	H	H	H	H	H	H	H	H	H	H	H	?	H

L = low risk of bias; H = high risk of bias; ? = unclear risk of bias

Figure 2.1: Study Selection Flow Chart



2.9 Supplementary Material

Supplementary Table 2.1: Search Strategy

PubMed search terms	EMBASE search terms
"diabetes mellitus"[MeSH Terms] OR diabet* AND "labor, obstetric"[MeSH] OR "labor"[tiab] OR "labour"[tiab] OR "parturition"[MeSH] OR "parturition"[tiab] OR "delivery, obstetric"[MeSH] OR intrapartum OR "peripartum period"[MeSH] OR "peripartum"[tiab] AND "glucose"[MeSH] OR “glucose”[tiab] OR glycemi* OR "insulins"[MeSH] OR “insulin”[tiab] OR “protocol”[tiab]	exp diabetes mellitus/ or diabetes * .tw. AND exp obstetric delivery/ or labour.tw. or exp labor/ or partuirition.tw. or exp birth/ or peripartum.tw. AND exp glycemic control/ or glycemi*.tw. or exp glucose blood level/ or exp glucose/ or exp insulin/ or insulin.tw. or protocol.tw. limit to human

Supplementary Table 2.2: Assessment of Study Quality

Area of potential bias	Classification procedure
Study participation	Quality item classified as present if all of the following criteria are met: 1) Source population or population of interest is adequately described 2) The sampling frame and recruitment are adequately described, possibly included methods to identify the sample, period of recruitment and place of recruitment. 3) Inclusion and exclusion criteria adequately described. 4) There is adequate participation in the study by eligible individuals. 5) The key baseline characteristics of study population are described.
Attrition	Quality item classified as present if one of the following criteria are met: 1) Response rate is adequate. 2) Reasons for lost to follow up are provided. 3) There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic factor measurement	Quality item classified as present if all of the following criteria are met: 1) A clear definition of in-target glucose control is provided. 2) Glucose is reported or appropriate (i.e. not data-dependent) cut-points are used. 3) The glucose measurement method is adequately valid and reliable to limit misclassification. 4) Adequate proportion of the study sample has complete data for intrapartum glycemic control. 5) The method and setting of measurement are the same for all study participants 6) Appropriate methods are used if imputation is used for missing glucose values.
Outcome measurement	Quality item classified as present if a clear definition of neonatal hypoglycemia was provided and applied uniformly across study participants.
Confounding measurement and account	Quality item classified as present if all of the following criteria met[1]: 1) Important confounders are measured. 2) The potentially important confounders were appropriately accounted for in the analysis.
Analysis	Quality item classified as present if all of the following criteria met: 1) There was sufficient presentation of data to assess the adequacy of the analysis. 2) The selected statistical model was adequate for the design of the study.

Adapted from Hayden et al. (40)

Chapter Three: **Neonatal hypoglycemia and intrapartum glycemic control in pregnancies complicated by Type 1, Type 2 and gestational diabetes**

3.1 Abstract

Aims/Hypothesis: To determine if in-target intrapartum glucose control is associated with neonatal hypoglycemia in women with Type 1, Type 2 and gestational diabetes.

Methods: This was a retrospective cohort study of pregnant women with Type 1, Type 2 and gestational diabetes and their neonates. Information was collected on consecutive women who attended specialized interdisciplinary clinics from 2009-2014 and database linkages were performed. The primary exposure was in-target glucose control defined as all capillary blood glucoses within 3.5 and 6.5 mmol/L during the intrapartum period. The primary outcome, neonatal hypoglycemia, was defined as treatment of the neonate with intravenous dextrose therapy. Multiple logistic regression was used to examine the association between maternal intrapartum glycemic control and neonatal hypoglycemia, adjusting for important covariates.

Results: A total of 6740 maternal infant pairs were included in this cohort study. 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 glycemic control was significantly associated with neonatal hypoglycemia 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 glycemic control was not significantly associated with neonatal hypoglycemia in women regardless of their type of diabetes.

Conclusions/interpretation: There was no significant association between in-target glycemic control and neonatal hypoglycemia after adjustment for neonatal factors. Given the high risk of maternal hypoglycemia and the resources required for intravenous insulin therapy, guidelines and future trials should consider whether more relaxed intrapartum glycemic targets may be safer in women with diabetes in pregnancy.

3.2 Background

Diabetes continues to be a common complication in pregnancy worldwide (1). Gestational diabetes accounts for most hyperglycemia in pregnancy and pre-existing diabetes, primarily Type 1 and Type 2, make up the remainder. Unfortunately, pregnancies in women with diabetes are associated with an increased risk of both maternal and fetal complications (4, 7, 61). Neonatal hypoglycemia is one such risk and is common in pregnancies with diabetes (8, 18, 61). Its definition is quite contentious, but is generally based on a blood glucose level, signs of hypoglycemia and/or need for treatment (14, 61).

The spectrum of neonatal hypoglycemia is wide and ranges from mild and easily treated hypoglycemia to severe and prolonged hypoglycemia requiring admission to the neonatal intensive care unit. Though its incidence varies depending on the population and definition used, neonatal hypoglycemia requiring intravenous dextrose is diagnosed in ~5-7% of offspring of women with gestational diabetes mellitus and ~25% of offspring of women with Type 1 diabetes (18, 30, 31). While there is little controversy that severe and untreated neonatal hypoglycemia can cause serious neurologic injury, more recent studies suggest that even treated neonatal hypoglycemia may be associated with neurodevelopmental impairment into childhood (21).

Current guidelines recommend intensive intrapartum glycemic control (target glucose of 4.0 to 7.0 mmol/L) based on the theory that this will decrease the risk of neonatal hypoglycemia by preventing a rise in fetal insulin in the hours prior to delivery (3, 33). Tight glycemic 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 hypoglycemia and increased resource utilization must also be weighed against the theoretical benefit of tight glycemic control in labour and delivery.

There are clear risk factors associated with neonatal hypoglycemia such as preterm delivery and large for gestational age (8, 61, 62). Most studies examining intrapartum glycemic control did not adjust for these factors which predate the short intrapartum period (34). For example, in both Type 1 and gestational diabetes, infant size and adiposity have been associated with neonatal hypoglycemia (8, 61, 62). 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 hypoglycemia. Large high quality studies are needed to address whether in-target intrapartum glycemic control is associated with neonatal hypoglycemia when considering important neonatal confounders.

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

3.3 Methods

We performed a retrospective cohort study of pregnant women with Type 1, Type 2 and gestational diabetes and their neonates. 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/).

3.3.1 Study population

Information was collected on consecutive women with a diagnosis of Type 1, Type 2 or gestational diabetes who attended specialized interdisciplinary clinics from January 1st, 2007 to December 31st 2014 in four tertiary care hospitals in Calgary, Alberta, Canada. Calgary is a city of ~1.4 million with an ethnically diverse population (63).

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

3.3.2 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 lab information systems for Calgary, Central and South Zone, all linked by a unique health identification number.

Most neonatal outcome and pregnancy data were obtained from the Alberta Perinatal Health Program database. The Alberta Perinatal Health Program (www.aphp.ca) database 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 (i.e. insulin, other diabetes medication, diabetes duration) 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 dieticians that provide diabetes care to these patients.

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 system used at all four hospitals). Laboratory data regarding antenatal glycemic control (i.e. HbA1c or oral glucose tolerance tests [OGTT] where available) were obtained from the lab 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. The data source for each variable included is summarized in Supplementary Table 3.1.

3.3.3 Local guidelines

All women with diabetes are to have a capillary glucose test at the onset of active labour (64). For women with Type 1 diabetes and Type 2 diabetes, glucose testing is recommended every 1 hours during active labour. For women with gestational diabetes, if they have a glucose <6.5 mmol/L in active labour, no additional testing, insulin, or endocrine consult is required. If women with gestational diabetes have 2 consecutive glucoses >6.5 mmol/L, an endocrine consult

is recommended for consideration of insulin treatment. Anyone on an intravenous insulin infusion requires hourly capillary glucose monitoring regardless of the type of diabetes.

Guidelines for the local screening and management of neonatal hypoglycemia recommend that all neonates of mothers with diabetes be screened within 30 minutes (65). Subsequent glucose testing is dependent upon initial glucose value. At minimum, it is recommended that repeat glucose testing is done every 1-2 hours before feeds until glucose stability is achieved in all infants at risk of hypoglycemia.

3.3.4 Definitions and outcome measures

The primary exposure of interest was intrapartum maternal glycemic control. The *a priori* definition of in-target glucose control was all capillary blood glucoses within 3.5 and 6.5 mmol/L during the intrapartum period. This is based on local clinical practice guideline targets and protocols. The intrapartum period was defined as up to 24 hours prior to delivery in keeping with the previously published literature (19, 62, 66). 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 hyperglycemia in labour (i.e. women with blood glucoses ≥ 8.6 mmol/L). Maternal hypoglycemia 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 but did not have a type of diabetes listed or 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 >91kg, smoking during pregnancy, pre-existing and gestational hypertension, diabetes medication, and insulin use. Trimester-specific HbA1c, was defined as the mean HbA1c for each trimester (conception to 12 weeks + 6 days, first trimester, 13 to 27 weeks + 6 days, second trimester and 28 weeks to term, third trimester).

Our *a priori* primary outcome, neonatal hypoglycemia, 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), birthweight and size for gestational age. Neonates were defined as large for gestational age, extreme large for gestational age and small for gestational age if their birth weight was >90^{th}, >97^{th} and <10^{th} percentile respectively based on national population references for age and sex (67).

3.3.5 Statistical analysis

Data were compared using chi-square tests for categorical variables and t-tests for continuous variables after assuring that assumptions of each test were met. An *a priori* decision was made to stratify all analyses by type of diabetes (Type 1, Type 2, and gestational). Multiple logistic regression was used to examine the association between maternal intrapartum glycemic control and neonatal hypoglycemia, adjusting for important 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 variable choice in the models. Additionally, we

considered the number of neonates with hypoglycemia 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, Version 14.1). A p-value of <0.05 was considered statistically significant.

3.4 Results

A total of 9686 maternal records were identified from the diabetes in pregnancy database (Figure 1). After database merging, exclusion of pregnancies not meeting inclusion criteria and the random selection of one pregnancy or neonate per woman, 8451 mother infant pairs were identified. Because the primary exposure, intrapartum glycemic 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 done until 2009. We therefore chose to exclude pregnancies prior to 2009. A total of 6740 maternal infant pairs were included in this cohort study.

Maternal characteristics by type of diabetes are displayed in Table 3.1. Of the 6740 women included, 182 had Type 1 diabetes, 350 had Type 2 diabetes and 6208 had gestational diabetes. Insulin was used in 182 (100%) women with Type 1 diabetes, 314 (89.7%) women with Type 2 diabetes and 1953 (31.5%) women with gestational diabetes. Intrapartum intravenous insulin infusion was used in 111 (61.0%) women with Type 1 diabetes, 58 (16.6%) women with Type 2 diabetes and only 61 (1.0%) women with gestational diabetes.

Neonatal characteristics are displayed in Table 3.2. The number of infants with neonatal hypoglycemia was 50 (27.5%), 64 (18.3%), and 313 (5.0%) for women with Type 1, Type 2, and gestational diabetes respectively. Infants of mothers with Type 1 diabetes were more likely to have neonatal complications including neonatal hypoglycemia, preterm delivery, neonatal intensive care unit admission, large for gestational age and extreme large for gestational age compared to women with Type 2 and gestational diabetes. Infants of mothers with gestational diabetes were least likely to have these complications.

3.4.1 Intrapartum glycemic 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 glycemic control data lost from database 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 examined for important differences between women with and without intrapartum testing (Supplementary Table 3.2). Women with Type 1 diabetes with and without intrapartum glycemic control data did not significantly differ. Women with Type 2 diabetes who had intrapartum testing had a significantly lower 3rd trimester HbA1c than women who did not (6.3 ± 0.8 vs 6.6 ± 1.0 respectively; p=0.007) but did not differ otherwise. Women with gestational diabetes who had intrapartum testing compared to 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-hour, and 2-hour glucoses on a 75g OGTT (Supplementary Table 3.2). They were

slightly more likely to have a neonate with hypoglycemia (5.6 vs 4.4%; p=0.04), though did not differ in other neonatal characteristics.

The mean number of capillary glucose tests performed for women with Type 1, Type 2, and gestational diabetes was 9.8 ± 7.6, 4.9 ± 4.7, and 1.8 ± 1.6 respectively. Hypoglycemia was more common in women with Type 1 diabetes with 56 (35.7%) women having at least one recorded glucose <3.5 mmol/L compared to 38 (14.2%) and 78 (2.4%) women with Type 2 and gestational diabetes respectively.

3.4.2 Intrapartum glycemic control and neonatal hypoglycemia

There was no significant difference in our primary exposure, in-target glucose control, in mothers of neonates with and without hypoglycemia with Type 1 and Type 2 diabetes (Table 3.3). However, in gestational diabetes, mothers of neonates with hypoglycemia were less likely to have in-target glucose control compared to mothers of neonates without hypoglycemia (69.8 vs 78.4% respectively; p=0.006).

For women with Type 1 diabetes, there were no significant differences in any of the either pre-specified or exploratory intrapartum glycemic variables between mothers of neonates with and without neonatal hypoglycemia. For women with Type 2 diabetes, mothers of neonates with hypoglycemia were more likely to have at least 50% and 25% of glucoses in-target as well, they had a lower percentage of tests within the target range compared to mothers of neonates without hypoglycemia. In contrast, for women with gestational diabetes all but percentage of tests below

target were significantly different in mothers of neonates with hypoglycemia compared to those without (Table 3.3).

Univariate analysis was used to examine for associations between maternal and neonatal characteristics and neonatal hypoglycemia (Supplementary Table 3.3). For women with Type 1 diabetes, large for gestational age, extreme large for gestational age, preterm delivery, HbA1c (1^{st}, 2^{nd} and 3^{rd} trimesters), male sex and maternal smoking were significantly associated with neonatal hypoglycemia (Supplementary Table 3.3). For women with Type 2 diabetes, extreme large for gestational age, preterm delivery, HbA1c in the 2^{nd} and 3^{rd} trimesters, and caesarean section were associated with neonatal hypoglycemia. For women with gestational diabetes, large for gestational age, extreme large for gestational age, preterm delivery, 2-hour OGTT glucose, pre-pregnancy weight >91kg, male sex and intrapartum glycemic control were associated with neonatal hypoglycemia.

After adjustment for important neonatal factors (large for gestational age, preterm delivery and infant sex), intrapartum in-target glycemic control was not significantly associated with neonatal hypoglycemia in women regardless of their type of diabetes (Table 3.4).

3.5 Discussion

We report on the largest cohort examining the relationship between intrapartum glycemic control and neonatal hypoglycemia in women with diabetes in pregnancy. We found that neonatal hypoglycemia was common in women with Type 1 diabetes (28%) and Type 2 diabetes (18%) but comparatively less common in women with gestational diabetes (5%). There were

differences in some intrapartum parameters between mothers with and without neonates with hypoglycemia in women with Type 2 and gestational diabetes. However, there was no significant association between in-target intrapartum glycemic control and neonatal hypoglycemia after adjustment for important neonatal factors regardless of the type of diabetes.

Our findings are consistent with some but not all studies examining the importance of glycemic control during labour and delivery as the literature in this area is conflicting (34). A recent systematic review highlighted the lack of high quality studies supporting the theory that tight intrapartum glycemic control may decrease the risk of neonatal hypoglycemia (34). Authors noted that lack of adjustment for known confounders was common in studies that identified a consistent and significant association between markers of glycemic control during labour and delivery and neonatal hypoglycemia. It is important to note that while our unadjusted analysis found many significant associations between intrapartum measures and neonatal hypoglycemia primarily in women with gestational diabetes, this significant association was no longer apparent after adjustment for important neonatal risk factors.

In contrast to our findings, a study by Joshi et al. which included women with pre-existing diabetes only (n=247) found the percentage of intrapartum tests between 7 to 10 mmol/L (OR 1.02; p=0.001) and 4 to 7 mmol/L (OR 0.99; p=0.02) were significantly associated with neonatal hypoglycemia even after adjustment for confounders (68). The difference in their findings may, at least in part, be explained by the different study definition of neonatal hypoglycemia used. Joshi et al. used a neonatal glucose 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 hypoglycemia, 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 glycemic control that were associated with neonatal hypoglycemia.

We found that antenatal glycemic control, as assessed with HbA1c, was associated with neonatal hypoglycemia in women with pre-existing diabetes in pregnancy. This association between antenatal glycemic control and risk of neonatal hypoglycemia has been found across populations (16, 62, 68). As well, our finding that infant size (either large for gestational and/or extreme large for gestational age) was associated with neonatal hypoglycemia in all types of diabetes is consistent with the available literature (8, 62, 69). Both findings support the hypothesis that factors occurring well before parturition pose a more substantial risk for the occurrence of neonatal hypoglycemia than intrapartum maternal glycemic control. The multicentre randomized controlled trial CONCEPTT (Continuous glucose monitoring in Type 1 diabetes pregnancy trial) randomized participants to continuous glucose monitoring (CGM) or standard capillary glucose monitoring. CONCEPTT found CGM significantly decreased the odds of neonatal hypoglycemia. As well, a higher time in-target as measured by CGM during the last half of pregnancy was associated with less neonatal hypoglycemia (18, 62). With only 15% of women using CGM during labour and delivery, it is unlikely this improvement in neonatal hypoglycemia in women using CGM was due to changes in the intrapartum period (62). When taken as a whole, it is likely that glycemic control in the months preceding delivery is an important and modifiable risk factor for neonatal hypoglycemia. With very few women able to achieve

guideline recommended glycemic targets, optimum glycemic control during pregnancy should continue to be an area of focus for women with diabetes, clinicians and researchers (4).

Neonatal hypoglycemia following pregnancies with gestational diabetes was relatively uncommon (5%) in this study and consistent with the literature using a similar definition including a low neonatal glucose and treatment with intravenous dextrose (30, 31). There were many significant differences between various intrapartum glycemic 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 important neonatal factors. Even if considering the unadjusted analyses alone, it is difficult to say if the significant differences between intrapartum glycemic control in mothers of neonates with and without hypoglycemia are clinically meaningful. In our cohort, only 7% of women with gestational diabetes (13 and 6% in mothers of neonates with and without hypoglycemia) had an actionable glucose (defined by our local protocol as two consecutive glucoses >6.5 mmol/L 1 hour apart) and only 1% of women with gestational diabetes received intravenous insulin therapy. Many more women may require intrapartum insulin therapy to decrease the risk of a relatively uncommon complication. Furthermore, our gold standard tool used to achieve in-target glycemic control in labour and delivery, intravenous insulin, lacks the precision to achieve tight glycemic targets (41). Additionally, the risk of maternal hypoglycemia when using intravenous insulin therapy is high and must be considered when weighing the risks and benefits (24, 34, 41).

Our study has several important strengths. This is the largest cohort examining the relationship between intrapartum glycemic control and neonatal hypoglycemia with the next largest cohort

including 733 women (50). Our primary outcome, exposures and analysis plan were published prior to data collection and any additional analyses are labelled as exploratory in nature. Our neonatal outcome data by type of diabetes are consistent with other large cohort studies and clinical trials which support the quality and accuracy of our dataset (4, 18, 30, 31).

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 glucoses were not measured and/or recorded on the clinical record. The differences between women with and without intrapartum data were minimal for those with pre-existing diabetes. Women with gestational diabetes who had intrapartum glucoses were more likely to be on insulin, had slightly higher OGTT glucoses, and were more likely to have a neonate with hypoglycemia. While this is the largest cohort to date, the adjusted ORs for in-target glycemic control and neonatal hypoglycemia were less than 1 (0.4 and 0.7 for women with type 1 and type 2 diabetes respectively), indicating that we may have been underpowered to detect a potentially important effect in these groups. Another limitation is our lack of a neonatal glucose cut off in our definition of hypoglycemia which may have led to the misclassification of neonates as having hypoglycemia 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 (18, 30, 31). 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 glycemic control and neonatal hypoglycemia after adjustment for neonatal factors in this large

retrospective cohort study. Neonatal hypoglycemia was significantly associated with risk factors such as large for gestational age and glycemic control that occur prior to the intrapartum period. Given the high risk of maternal hypoglycemia and the resources required for intravenous insulin therapy, guidelines and future trials should consider whether more relaxed intrapartum glycemic targets may be safer in women with diabetes in pregnancy.

3.6 Acknowledgements

We would like to thank Susan Crawford, Epidemiologist at Alberta Perinatal Health Program and Carolyn Oldford, Research Coordinator at the Diabetes in Pregnancy Foothills Medical Centre Clinic. Our study was supported by funding from the Stewart Diabetes Fund (Alberta, Canada) and the Cal Wenzel Cardiometabolic Fund.

3.7 Contribution

JY, LD, KM and SW conceived and designed the study. JY collected the data with the help of Susan Crawford. JY analyzed the data. JY, LD, KM and SW interpreted the data. JY prepared the manuscript, which all authors critically reviewed. All authors have given final approval of the version to be published. JY is the guarantor of this work, had full access to all the study data and takes responsibility for the integrity of the data.

3.8 Tables and Figures

Table 3.1: Maternal Characteristics by Type of Diabetes

	Type 1 Diabetes	Type 2 Diabetes	Gestational Diabetes
	n=182	n=350	n=6208
Maternal Characteristics*			
Maternal age in years	30.1 ± 5.0	33.7 ± 5.0	33.0 ± 4.9
Duration of diabetes	14.9 ± 8.4	4.0 ± 4.2	-
Primiparous	108 (59.3)	127 (36.3)	2469 (39.8)
Pre-pregnancy weight >91kg	16 (8.8)	126 (36.0)	742 (12.0)
Smoking	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 Glycemic Control**			
HbA1c			
1st trimester	7.6 ± 1.4	7.1 ± 1.5	-
2nd trimester	6.8 ± 0.9	6.3 ± 0.8	-
3rd trimester	6.9 ± 0.8	6.3 ± 0.9	-
Glucose Screen (50g)			
1-hour			9.6 ± 1.6
Oral Glucose Tolerance Test (75g)			
Fasting	-	-	4.8 ± 0.8
1-hour	-	-	10.7 ± 1.3
2-hour	-	-	9.0 ± 1.5

Data are presented as counts (percentages) or means ± standard deviation; *Diabetes duration available for 173 women with Type 1 diabetes and 314 women with Type 2 diabetes; Parity missing on 6 records; Smoking and hypertension missing on 9 records; **Trimester specific HbA1c was available for 160-173 women and 241-290 women with Type 1 and Type 2 diabetes respectively; Glucose screen data was available for 5664 women with gestational diabetes; Oral glucose tolerance test data were available for 3476-4259 women with gestational diabetes.

Table 3.2: Neonatal Characteristics by Type of Diabetes

	Type 1 Diabetes	Type 2 Diabetes	Gestational Diabetes
	n=182	n=350	n=6208
Neonatal Characteristics*			
Neonatal hypoglycemia (IV 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	3474.3 ± 679.7	3241.3 ± 680.7	3229.3 ± 551.8
Large for gestational age	88 (48.4)	83 (23.7)	602 (9.7)
Extreme 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)

Data are presented as counts (percentages) or means ± standard deviation; *Neonatal intensive care unit admission missing on 6 records; birthweight information missing on 1 record

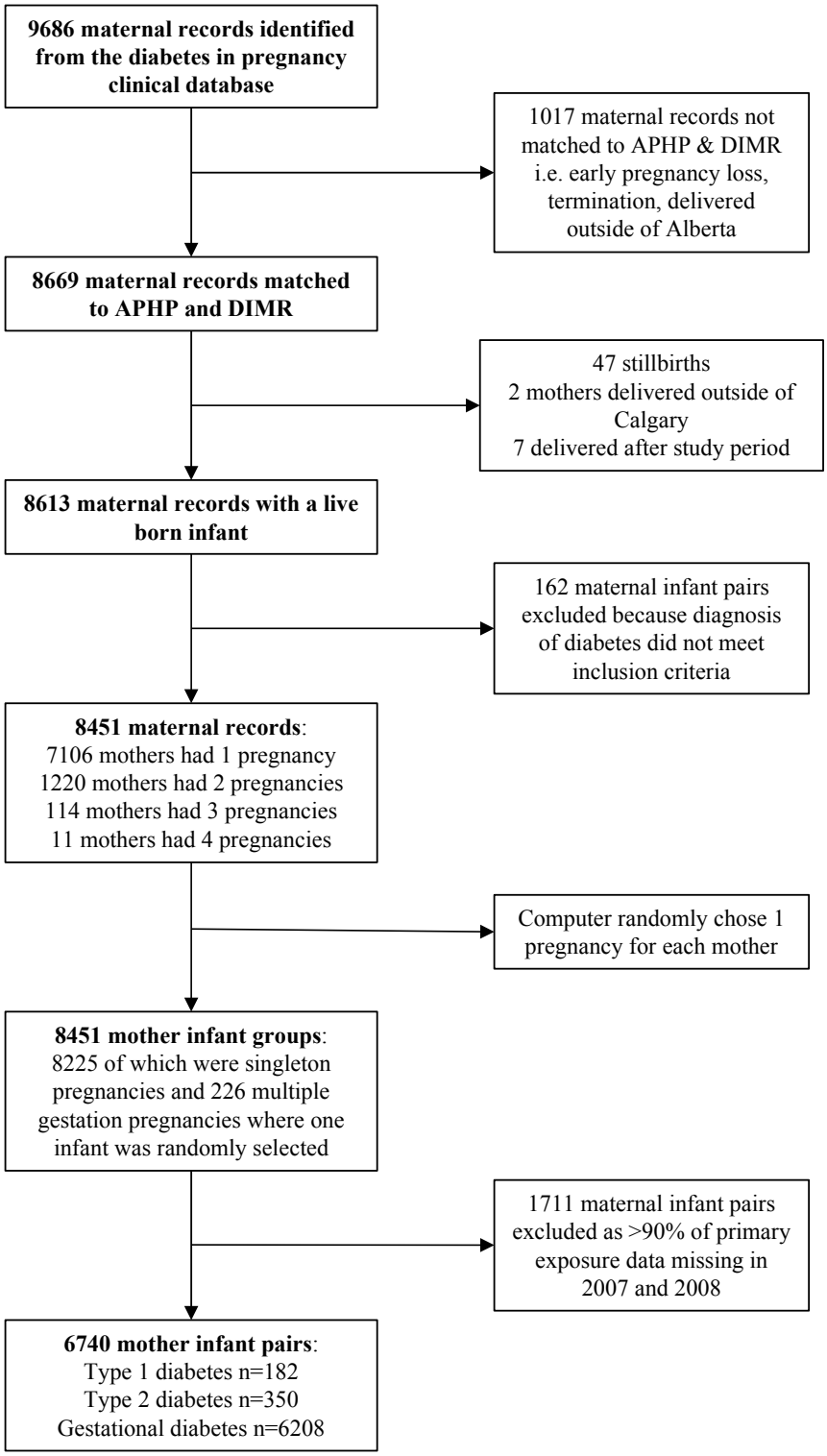
Table 3.3: Intrapartum (within 24 hours prior to delivery) Glycemic Control for Mothers of Neonates with and without Hypoglycemia by Type of Diabetes

	Type 1 Diabetes			**Type 2 Diabetes**			**Gestational Diabetes**		
	n=157			n=267			n=3256		
	Neonatal Hypoglycemia	No Neonatal Hypoglycemia		Neonatal Hypoglycemia	No Neonatal Hypoglycemia		Neonatal Hypoglycemia	No Neonatal Hypoglycemia	
	n=47	n=110	p-value	n=46	n=221	p-value	n=182	n=3074	p-value
Pre-specified									
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 hyperglycemia	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	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	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**

Table 3.4: Adjusted Multivariable Logistic Regression Models for Odds of Neonatal Hypoglycemia

	Adjusted Model	
	Odds Ratio (95% CI)	**p-value**
Type 1 Diabetes		
In-target glycemic 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 glycemic 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 glycemic 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

Figure 3.1: Study Flow Chart



3.9 Supplementary Material

Supplementary Table 3.1: Summary of the Data Source for Included Variables

Source Database	Variables
Alberta Perinatal Health Database	• Neonatal sex • Mode of delivery • Birth gestational age • Admission to the neonatal intensive care unit • Birthweight • Maternal age • Pre-pregnancy weight >91kg • Maternal smoking • Pre-existing hypertension • Hypertension
Diabetes in Pregnancy Clinical Database	• Type of diabetes • Duration of diabetes • Treatment during pregnancy (insulin, metformin, other) • Insulin pump use
Analytics (including Sunrise Clinical Management System)	• Neonatal hypoglycemia (received intravenous dextrose treatment) • Capillary glucose testing in labour and delivery • Intravenous insulin treatment during labour and delivery
Lab Information Systems for Calgary, Central and South Zone	• HbA1c • 50g glucose challenge • 75g oral glucose tolerance test

Supplementary Table 3.2: Differences Between Women with and without Intrapartum Glycemic Control Data

	Type 1 Diabetes			**Type 2 Diabetes**			**Gestational Diabetes**		
	Intrapartum data	No intrapartum data		Intrapartum data	No intrapartum data		Intrapartum data	No intrapartum data	
	n=157	n=25	p-value	n=267	n=87	p-value	n=3256	n=2952	p-value
Maternal age	30.1 ± 5.1	30.0 ± 4.3	0.92	33.6 ± 5.0	34.0 ± 4.9	0.50	**32.8 ± 4.9**	**33.2 ± 4.9**	**0.0007**
Insulin use	157 (100)	25 (100)	-	243 (91.0)	71 (85.5)	0.15	**1378 (42.3)**	**575 (19.5)**	**<0.0001**
Mean HbA1c*									
1st Trimester	7.6 ± 1.5	7.5 ± 1.0	0.63	7.2 ± 1.5	6.9 ± 1.3	0.28	-	-	-
2nd Trimester	6.9 ± 1.0	6.8 ± 0.6	0.64	6.3 ± 0.9	6.3 ± 0.7	0.76	-	-	-
3rd Trimester	6.9 ± 0.8	6.8 ± 0.6	0.53	**6.3 ± 0.8**	**6.6 ± 1.0**	**0.007**	-	-	-
OGTT (75g)**									
Fasting	-	-	-	-	-	-	**4.9 ± 0.8**	**4.7 ± 0.7**	**<0.0001**
1-hour	-	-	-	-	-	-	**10.8 ± 1.3**	**10.6 ± 1.3**	**<0.0001**
2-hour	-	-	-	-	-	-	**9.1 ± 1.5**	**8.9 ± 1.5**	**0.02**
Neonatal hypoglycemia	47 (29.9)	3 (12.0)	0.06	46 (17.2)	18 (21.7)	0.36	**182 (5.6)**	**131 (4.4)**	**0.04**
Male	87 (55.4)	12 (48.0)	0.49	139 (52.1)	45 (54.2)	0.73	1731 (53.2)	1526 (51.7)	0.25
Preterm	62 (39.5)	12 (48.0)	0.42	48 (18.0)	21 (25.3)	0.14	356 (10.9)	318 (10.8)	0.83
Large for gestational age	74 (47.1)	14 (56.0)	0.41	58 (21.7)	25 (30.1)	0.12	336 (10.3)	266 (9.0)	0.08

Data are presented as counts (percentages) or means ± standard deviation; *Trimester specific HbA1c was available for 160-173 women and 241-290 women with Type 1 and Type 2 diabetes respectively; **Oral glucose tolerance test data were available for 3476-4259 women with gestational diabetes; OGTT, oral glucose tolerance test

Supplementary Table 3.3: Results of Univariate Logistic Regression for Neonatal Hypoglycemia

Type 1 Diabetes

Variable	Odds Ratio (95% CI)	p-value
Large for gestational age	3.4 (1.7, 7.0)	<0.0001
Extreme large for gestational age	3.4 (1.7, 6.8)	0.001
Preterm	3.4 (1.7, 6.6)	<0.0001
First trimester HbA1c	1.4 (1.1, 1.8)	0.004
Second trimester HbA1c	2.1 (1.4, 3.1)	<0.0001
Third trimester HbA1c	2.2 (1.4, 3.4)	0.001
Pump use in pregnancy	1.4 (0.7, 2.9)	0.30
Caesarean section	1.6 (0.8, 3.1)	0.20
Maternal age at delivery	1.0 (0.9, 1.0)	0.18
Pre-pregnancy weight >91kg	0.4 (0.1, 1.6)	0.18
Smoking	2.6 (1.1, 6.2)	0.04
Sex (male)	2.2 (1.1, 4.3)	0.03
Intrapartum Variable		
In-target glycemic control	0.6 (0.20, 1.6)	0.30

Type 2 Diabetes

Variable	Odds Ratio (95% CI)	p-value
Large for gestational age	1.6 (0.88, 2.9)	0.12
Extreme large for gestational age	2.8 (1.3, 5.8)	0.007
Preterm	3.5 (1.9, 6.4)	<0.0001
First trimester HbA1c	1.2 (1.0, 1.4)	0.14
Second trimester HbA1c	1.5 (1.1, 2.1)	0.009
Third trimester HbA1c	1.6 (1.2, 2.2)	0.003
Caesarean section	2.0 (1.1, 3.6)	0.02
Maternal age at delivery	1.0 (1.0, 1.0)	0.28
Pre-pregnancy weight >91kg	0.9 (0.5, 1.6)	0.77
Smoking	1.9 (0.9, 4.3)	0.10
Sex (male)	1.2 (0.7, 2.1)	0.52
Intrapartum Variable		
In-target glycemic control	0.6 (0.3, 1.2)	0.18

Gestational Diabetes

Variable	Odds Ratio (95% CI)	p-value
Large for gestational age	1.8 (1.3, 2.5)	<0.0001
Extreme large for gestational age	2.2 (1.4, 3.5)	0.001
Preterm	6.4 (5.0, 8.1)	<0.0001
Gestational screen (50g)		
1-hour	1.0 (1.0, 1.1)	0.46
Oral Glucose Tolerance Test (75g)		
Fasting	1.1 (0.9, 1.3)	0.56
1-hour	1.0 (0.9, 1.2)	0.44
2-hour	1.1 (1.0, 1.2)	0.02
Caesarean section	1.8 (1.4, 2.2)	<0.0001
Maternal age at delivery	1.0 (1.0, 1.0)	0.07
Pre-pregnancy weight >91kg	1.4 (1.0, 2.0)	0.03

Smoking	1.2 (0.7, 1.8)	0.51
Sex (male)	1.4 (1.1, 1.8)	0.002
Intrapartum Variable		
In-target glycemic control	0.6 (0.5, 0.9)	0.007

Chapter Four: **Summary**

4.1 Overview

In 1989, a group of stakeholders met in St. Vincent's, Italy to develop a set of goals to reach for people with diabetes (70). Named the St. Vincent's Declaration, one of its five year targets was to "achieve pregnancy outcomes in the diabetic woman that approximates that of the non-diabetic woman". Unfortunately, almost 30 years later, we remain far from closing the gap between optimal pregnancy outcomes and those in women with diabetes in pregnancy (4). Neonatal hypoglycemia remains a common, theoretically preventable, and potentially serious complication of diabetes in pregnancy; as researchers and clinicians, we continue to search for ways to fulfill the promise made many years ago.

Intrapartum glycemic control is an attractive target when aiming to decrease the risk of neonatal hypoglycemia. Though it varies from person to person, much of the labour and delivery period occurs in hospital, a theoretically controlled setting. It is a discrete amount of time in which women are taking little in by mouth (not eating or drinking) and with the use of intravenous insulin therapy, we may be able to strive for perfection during this period. However, even in this highly monitored setting using the current gold-standard intravenous insulin, we fall short of perfection.

The intrapartum period is a time of dramatic and dynamic changes in hormones, glucose utilization and insulin sensitivity (71). Intravenous insulin infusion is, by its nature, reactive which limits its ability to achieve tight glycemic targets (4.0-7.0 mmol/L). Furthermore, maternal hypoglycemia is commonplace, with 36% of women with Type 1 diabetes in our cohort having

at least one glucose <3.5 mmol/L. The results of this thesis call to question this dogmatic approach to the intrapartum period.

'*Primum non nocere'*, first do no harm, a principle of medical ethics and the title of a letter to the editor written regarding our systematic review (Chapter 2) (34, 72). The authors of this letter argue that in the absence of compelling evidence of the benefit of strict glycemic control they ask the guidelines to "urgently review the dictum that peripartum plasma glucose should be maintained between 4 and 7 mmol/L" (72). Additionally, our review was highlighted as an Editor's Selection in the special issue "Clinical aspects of diabetes in pregnancy", where too the editor also urged policy makers to "re-consider these targets" given the risk of maternal hypoglycemia and resource implications (73). These publications, and others, highlight the topicality of this issue in the clinical diabetes community (72-75).

When taking the results of this thesis in its entirety, we cannot rule out that tight intrapartum glycemic control is associated with neonatal hypoglycemia, especially with its varying definitions. However, this must be carefully weighed against the risk of maternal hypoglycemia, the demands on busy ward staff, and the invasive nature of intravenous insulin treatment. In addition, we along with others have other important targets we can strive for, namely improving antenatal glycemic control and reducing large for gestational age or extremely large for gestational age neonates. These have been shown across well-powered studies to be associated with an increased risk of neonatal hypoglycemia in women with pre-existing diabetes in pregnancy (8, 16, 18, 62). While we have demonstrated that infant size is associated with risk of neonatal hypoglycemia in women with gestational diabetes, it is unclear if glycemic control

during the third trimester plays a role, since we lack that data. Indeed, it may be more reasonable to separate the discussion of neonatal hypoglycemia by type of diabetes as the magnitude of risk and role of treatment differ substantially.

4.2 Neonatal hypoglycemia and gestational diabetes

The prevalence of neonatal hypoglycemia in a low risk population is difficult to assess given the varying definitions. Using a low glucose alone, the incidence may range from 5-15% in the low risk neonate (15). Our cohort study included 6208 women with gestational diabetes, 3256 of whom had intrapartum glycemic control data, by far the largest cohort to date. Neonatal hypoglycemia was relatively uncommon, with only 5% of neonates of mothers with gestational diabetes receiving intravenous dextrose. Given the time period of our cohort study, it is unlikely that this represents a shift towards treatment with dextrose gel rather than intravenous dextrose that has occurred more recently (76). Unfortunately, our cohort study did not include women without diabetes, so we cannot comment if the incidence of neonatal hypoglycemia is above that of the general population in Calgary.

In the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) landmark cohort study defining gestational diabetes, maternal glucose levels were only weakly associated with neonatal hypoglycemia (OR 1.01-1.14 for 1 SD higher OGTT glucose levels) (61). Like our results, the 2-hour OGTT glucose was more strongly associated with neonatal hypoglycemia, but the effect size was still small (OR 1.1; p=0.02). As all women with gestational diabetes were seen in our interdisciplinary diabetes in pregnancy clinic, they would have received some form of treatment for their diabetes. This would be primarily in the form of dietary and lifestyle recommendations

which is the mainstay of treatment of gestational diabetes (3). An additional ~one third of women in our cohort with gestational diabetes required insulin therapy. Interestingly, a high quality meta-analysis failed to show any effect of treatment of gestational diabetes on neonatal hypoglycemia (pooled risk ratio 1.18 [95% CI 0.92, 1.52]) (12).

If we were to postulate neonatal hypoglycemia was indeed more common in our cohort of women with gestational diabetes, the increased risk may be due to additional risk factors that are more common in women with gestational diabetes such as obesity or gestation hypertension rather than hyperglycemia itself causing the increased risk (3). It is interesting that our univariate analysis demonstrated pre-pregnancy weight >91kg was significantly associated with neonatal hypoglycemia (OR 1.4; p=0.03) in women with gestational diabetes, but not in women with pre-existing diabetes. Unfortunately, the BMI data from our diabetes in pregnancy clinical database were incomplete and could not be used in our analysis. In other studies, both obesity and excess gestational weight gain have been associated with increased risk of neonatal hypoglycemia (60, 77). Pathophysiologically, this could be explained through the maternal over-nutrition seen in obesity causing fetal hyperinsulinemia, which subsequently causes an increased risk of neonatal hypoglycemia.

The potential importance of maternal weight and weight gain in the risk of neonatal hypoglycemia in women with gestational diabetes should be considered in strategies aimed at decreasing the incidence of neonatal hypoglycemia. When added to the conclusions of both our systematic review and retrospective cohort study regarding the lack of a significant association of intrapartum glycemic control in women with gestational diabetes, maternal weight and

nutrition may be a more lucrative target when trying to decrease the risk of neonatal hypoglycemia than improving the already high proportion of women with in-target intrapartum glycemic control.

4.3 Neonatal hypoglycemia and pre-existing diabetes – Shifting the focus back to antenatal glycemic control

A large nationwide cohort in the UK found that only 40 and 76% of women with Type 1 and 2 diabetes respectively achieved target glycemic control (HbA1c <6.5%) late in pregnancy despite hard work of women with diabetes and the support of interdisciplinary healthcare teams (4). Even in a randomized controlled trial setting with the help of continuous glucose monitoring technology, women with Type 1 diabetes spend almost eight hours a day outside of the target glucose range (18). This leaves much room for improvement in antenatal glycemic control in women with pre-existing diabetes in pregnancy.

Our cohort study found glycemic control in women with Type 1 and 2 diabetes in the 2nd and 3rd trimesters, as assessed by HbA1c, was significantly associated with neonatal hypoglycemia in the univariate analysis. This association of neonatal hypoglycemia with antenatal glycemic control has been shown previously in studies of women with pre-existing diabetes (16, 62, 68). Additionally, target glycemic control prior to and during pregnancy (typically defined as a HbA1c <6.5%) has been shown across many studies and populations to not only improve common pregnancy outcomes such as large for gestational age and neonatal intensive unit admissions but also serious adverse outcomes such as congenital anomaly, stillbirth and early neonatal death (16, 78-80). In the same UK cohort described above, authors noted that in women

with Type 1 and 2 diabetes respectively, 40 and 22% had preterm deliveries, as well, 46 and 24% had large for gestational age neonates (4). These numbers are nearly identical to our cohort where we found that in women with Type 1 and 2 diabetes respectively, 41 and 20% delivered preterm and 48 and 24% had a large for gestational age neonate. We must continue to develop better strategies to help improve measures of glycemic control in women with pre-existing diabetes.

We were unable to demonstrate a significant difference in neonatal hypoglycemia with in-target glycemic control in women with Type 1 and 2 diabetes after adjustment for known neonatal confounders. Given the strength of the available evidence regarding maternal antenatal glycemic control in addition to the lack of high quality evidence consistently supporting an association between intrapartum maternal glucose and neonatal hypoglycemia, focus should continue to be on helping women to achieve antenatal glucose targets. Improving antenatal glycemic control should improve the identified risk factors for neonatal hypoglycemia (large for gestational age and preterm delivery) in addition to any independent association in-target glycemic control may have.

4.4 Conclusions and future directions

When the results of our cohort study are added to those of our systematic review, the weight of the evidence suggests there is no significant consistently reproducible association between in target intrapartum glycemic control and neonatal hypoglycemia. By the observational nature of the included studies, we cannot comment on whether more relaxed glycemic targets may be safer in women with diabetes in pregnancy. A randomized controlled trial which directly compares

current/tight glycemic targets (4.0-7.0 mmol/L) to more relaxed targets (for example 5.0-10.0 mmol/L) would be required to determine if a more relaxed approach may be safer for women with diabetes without increasing the risk of neonatal hypoglycemia. Knowing the incidence of neonatal hypoglycemia in women with gestational diabetes and the proportion of women who already achieve in-target glycemic control without intravenous insulin therapy, an argument could be made against the inclusion of women with gestational diabetes in a clinical trial.

Improving antenatal glycemic control in women with pre-existing diabetes in pregnancy remains an important goal. Certainly, if we are to meet the goal set forth by the St. Vincent Declaration, near-perfect glycemic control for all women with diabetes would need to be achieved (70). Unfortunately, our current tools fall short of providing women with the glycemic control needed to decrease the risk associated with pre-existing diabetes in pregnancy (81). It will take everything in our diabetes armamentarium as well as tools not yet universally available to achieve pregnancy outcomes that approximate those of women without diabetes.

Automated insulin delivery (also known as closed-loop insulin delivery and the bionic pancreas) is a technology currently not available in pregnancy outside of clinical trials (19, 66, 82, 83). This technology is likely required to standardize diabetes care. In other words, to all help women with diabetes achieve target glycemic control in a way that is not all consuming. Automated insulin delivery may also help us achieve near perfect glycemic control in hospital in a way that does not increase the maternal hypoglycemia that is so commonplace with the use of intravenous insulin therapy. Until this technology is effective, affordable and universally available, we must

continue to support all women with diabetes to the best of our abilities. This includes protecting them from unnecessary harm.

Until we have either the results from randomized controlled trials supporting the use of tight intrapartum glycemic targets and/or universally available automated insulin delivery for intrapartum management, we urge guidelines writers and policy makers to consider more relaxed glycemic targets in the intrapartum period. William Osler wisely said "*the greater the ignorance the greater the dogma*"; since evidence has replaced ignorance, so too should we challenge the dogma.

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