STUDY PROTOCOL

PRECeDe Trial: Prevention of neonatal Respiratory distress with antenatal corticosteroids prior to Elective Caesarean section in women with diabetes – A Randomised Trial

Protocol Number: 1
Version: 3
Date: 06/10/2022
Trial Registration: TBC
Sponsor: The University of Melbourne
Coordinating Centre: Western Health

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Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

SUMMARY OF AMENDMENTS

DATE	PROTOCOL VERSION	AMENDMENT TYPE	SUMMARY OF CHANGES MADE
4/8/2022	2	RESPONSE TO HREC QUERIES	• Minor clarifications made to primary aim and primary outcome to improve clarity and consistency • Modification of criteria to classifyseverity of respiratory morbidity • Clarification of timeframes for Health Economics assessments • Clarification of analyses to be undertaken by DMC and roles of DMC • Inclusion of Western Health as the Coordinating centre
06.10.2022	3	RESPONSETO QUERIES: Change of Redcap Data storage from University of Auckland server to University of Melbourne server	All identifiable and re-identifiable data will now be stored on a secure password protected server located within the University of Melbourne. These data will no longer be stored within the University of Auckland.

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STUDY SYNOPSIS

Title:	PRECeDe Trial: **P**revention of neonatal **R**espiratory distress with antenatal corticosteroids prior to **E**lective **C**aesarean section in women with **D**iabetes - A Randomised Trial
Short Title:	PRECeDe RCT
Design:	Triple blind, placebo controlled, randomised controlled trial (RCT) to assess whether antenatal corticosteroids reduce the incidence of neonatal respiratory distress when given to women with diabetes prior to an elective caesarean section (CS) planned between 35^{+0} and 39^{+6} weeks' gestation.
Study Question:	Does administration of antenatal corticosteroids to women with pre-gestational or gestational diabetes where birth by elective CS is planned between 35^{+0} weeks and 39^{+6} weeks of gestation, reduce neonatal respiratory morbidity without adverse consequences for mother or baby?
Primary Objective:	To determine whether administering antenatal corticosteroids to women with either pre-gestational or gestational diabetes who plan to give birth by elective CS between 35^{+0} weeks and 39^{+6} weeks' gestation reduces the rate of neonatal respiratory morbidity requiring admission to the neonatal nursery and any form of respiratory support (e.g. intermittent positive pressure via an endotracheal tube, nasal continuous positive airway pressure (CPAP), Hi- or Lo-flow oxygen/air mixture, or increased ambient oxygen delivered into an incubator) for ≥60 minutes at any time following birth.
Secondary Objectives:	1. To determine whether administering antenatal corticosteroids to women with either pre-gestational or gestational diabetes who plan to give birth by elective CS between 35^{+0} weeks and 39^{+6} weeks' gestation: • increases the rate of short-term non-respiratory morbidity (eg neonatal hypoglycaemia, neonatal nursery admission and length of stay) in the infant; • increases the rate of maternal morbidities (eg maternal hyperglycaemia, infection); • has a favourable cost-effectiveness ratio 2. To assess the extent to which participants, clinicians and researchers remain blinded to the treatment allocation (in a subset of participants). 3. To establish a cohort of children to evaluate the longer term outcomes at 2 years, 6-7 years and 10-12 years following corticosteroid exposure in infants

	of mothers with diabetes (including cardiovascular, respiratory, metabolic, and neurocognitive function).
Inclusion Criteria:	Women with a singleton or twin pregnancy who have a planned elective CS scheduled between 35^{+0} and 39^{+6} weeks' gestation who have pre-gestational diabetes OR gestational diabetes (diagnosed on a pregnancy 75 g oral glucose tolerance test according to the national Australian or New Zealand criteria for gestational diabetes (GDM) or via the modified criteria for diagnosis of GDM during the COVID-19 pandemic recommended by the Royal Australian New Zealand College of Obstetricians and Gynaecologists and Australasian Diabetes in Pregnancy Society) AND plan to give birth by elective CS within the next 7 days, between 35^{+0} and 39^{+6} weeks gestation (randomisation can occur within the week prior to 35^{+0} weeks as long as the CS is scheduled on or after 35^{+0} weeks gestation)
Exclusion Criteria:	1. Known major fetal anomaly or chromosomal anomaly. 2. Administration of intramuscular antenatal corticosteroid therapy for fetal lung maturation at any time during the pregnancy prior to randomisation. 3. Maternal systemic fungal infection 4. Maternal thrombocytopaenia with platelet count below $80x10^9$ /litre 5. Hypersensitivity to betamethasone sodium phosphate, betamethasone acetate, or other corticosteroids 6. Other contraindication to corticosteroids 7. Previous participation in the PRECeDe trial (prior participation in the PRECeDe Pilot trial is NOT regarded as an exclusion from participation in the current trial)
Number of Planned Subjects:	2200 mothers (and their infants)
Investigational product:	11.4 mg of Celestone Chrondose in 2ml (betamethasone 11.4 mg, as betamethasone sodium phosphate and betamethasone acetate)

	Two injections will be administered intramuscularly, 24 hours apart, to participants randomised to receive the investigational product.
Placebo	Normal saline in an identical appearing syringe.
Safety considerations:	Betamethasone is used extensively as part of the antenatal care in women at risk of giving birth prematurely. There is abundant literature supporting the safety of this drug in pregnant women. Betamethasone is associated with maternal hyperglycaemia and has been reported in one study to increase the risk of neonatal hypoglycaemia. Observational studies have reported an increase in the risk of mild adverse neurocognitive outcomes (eg learning problems) in children who were exposed to antenatal corticosteroids prior to 35^{+0} weeks but were subsequently born at term. There are no studies evaluating the long term neurocognitive outcomes of children exposed to corticosteroids after 35^{+0} weeks and who birthed within 7 days of corticosteroid exposure. There are currently no other safety concerns with respect to this drug.
Statistical Methods:	Outcomes will be compared between the intervention and control groups using an intention-to-treat analysis. For all binary outcomes the magnitude of the between-group differences will be quantified by fitting a logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for the corresponding population OR, stratified by site, type of diabetes (Type 1 diabetes, Type 2 Diabetes, Gestational Diabetes), and gestation at planned elective CS (35^{+0} to 36^{+6} weeks, 37^{+0} to 38^{+6} and 39^{+0} to 39^{+6} weeks). Linear regression will be used for non-categorical outcomes. For infant outcomes, models will be fitted using Generalised Estimating Equations to allow for non-independence of outcomes among twins from the same pregnancy.
Trial Registration:	The trial is registered with ANZCTR TBC
Funding:	NHMRC Clinical Trials and Cohort Studies Grant 2014750 (CIA Said)

1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
AE	Adverse Event
ACS	Antenatal Corticosteroids
ALPS	Antenatal Betamethasone for women at Risk for Late Preterm Delivery
ASTECS	Antenatal Steroids for Term Caesarean Section
AQuOL-8D	Assessment of Quality of Life
BGL	Blood Glucose Level
CI	Confidence Interval
CPAP	Contnuous positive airway pressure
CRF	Case Report Form
CS	Caesarean section
EPDS	Edinburgh Postnatal Depression Scale
FiO_2	Fractional Inspired oxygen
GDM	Gestational Diabetes Mellitus
Hi-Flow	High flow gas delivered via nasal cannulae
HMD	Hyaline membrane disease
HR	Hazard Ratio
Lo-Flow	Low flow gas delivered via nasal cannulae
MAP	Mean airway pressure
MRI	Magnetic Resonance Imaging
OR	Odds ratio
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
RR	Relative Risk
RWH	Royal Women's Hospital
SAE	Serious Adverse Event
SF12	12 Item Short form Survey
SUSAR	Serious Unexpected Adverse Reaction
TTN	Transient Tachypnoea of Newborn
WH	Western Health

2. STUDY SITES

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3. INTRODUCTION/BACKGROUND INFORMATION

3.1 LAY SUMMARY

Administration of antenatal corticosteroids to women prior to preterm birth has been one of the greatest success stories of modern pregnancy and newborn care. Multiple studies have demonstrated a reduction in the rate of breathing problems in newborn babies after this treatment. More recently, several studies have reported benefits when antenatal corticosteroids are given to women who give birth by elective caesarean section (CS) after 35 weeks' gestation. Elective CS (planned CS performed prior to the onset of labour), as opposed to vaginal birth (or even CS in labour) is associated with greater risks of breathing problems in newborn infants and this results in longer hospital stays and separation from the mother. Women with diabetes were specifically excluded from the studies that have demonstrated improvements in the rate of newborn breathing problems, hence, whether these benefits are the same for infants born to women with diabetes is uncertain. Moreover, women with diabetes are more likely to give birth by caesarean section and to require birth at earlier gestations compared with women who do not have diabetes, and their infants are more likely to have breathing problems because they are more likely to lack a lining substance in their lungs called "surfactant" that is required to prevent the airspaces in the lung from collapsing after birth. Further research in women with diabetes during pregnancy is urgently needed as these women and their infants potentially have the most to gain from this intervention, if it is indeed effective.

This multicentre, randomised, placebo controlled trial is designed to investigate the outcomes for the mother and baby following antenatal administration of corticosteroids within 7 days prior to elective CS in women with pre-gestational or gestational diabetes. We will also determine whether this simple intervention is good value for money and maintain contact with participants so that we can undertake follow-up studies to assess the longer term outcomes of this intervention.

Given the increasing rates of both diabetes and CS, this trial will provide the information clinicians need to provide the best possible care for women with diabetes who are undergoing a planned CS.

3.2 INTRODUCTION

The prevalence of diabetes in pregnancy, particularly gestational and Type 2, is increasing rapidly worldwide. The International Diabetes Federation reported that 20.4 million (1 in 6) livebirths were affected by diabetes globally in 2019,[5] while over 33,000 pregnant women were affected in Australia alone in 2019.[6] In 2020, 25.2% of women giving birth at Western Health, Melbourne, had either pre-gestational (Type 1 or Type 2 diabetes diagnosed prior to pregnancy) or gestational diabetes, compared with only 4.9% in 2011; a 5.1 fold increase in just 10 years. Birth by CS is also increasing, with one-third of all babies in Australia now born by CS.[6] CS is more likely in women with a pregnancy complicated by all types of diabetes[7-9] compared with women without diabetes; odds ratio (OR) for CS in women with gestational diabetes is 1.4 (95% confidence interval (CI) 1.4, 1.5), for Type 1 Diabetes 4.3 (95% CI 3.8, 4.8), and for Type 2 Diabetes 3.2 (95% CI 2.9, 3.5).[9]

Respiratory morbidity, caused by either Respiratory Distress Syndrome (RDS) due to surfactant deficiency or Transient Tachypnoea of the Newborn (TTN) occurs more frequently in infants born to women with diabetes,[7-9] and in those born by CS.[3]

Fortunately, death from RDS in babies born at or near term is uncommon. However, respiratory morbidity in term or near-term babies results in separation from the mother, invasive treatments such as assisted ventilation, prolonged hospitalisation, and lower rates of breast feeding.[10] Giving antenatal corticosteroids to women before preterm birth substantially reduces neonatal mortality and morbidity,[11] and is good value for money.[12] However, it is uncertain if antenatal corticosteroids given prior to elective CS (CS prior to labour onset) during the late pre-term/term period reduce respiratory morbidity.[1,13,14] While previous studies have suggested a beneficial effect of corticosteroids on respiratory morbidity when given prior to elective CS, the validity of these prior trials has been questioned[15] and one of these trials has recently been retracted following concerns about data integrity.[2,4] Furthermore, concerns have been raised about the risks of neonatal hypoglycaemia[16] and long term adverse neurological outcomes for infants born late preterm or at term who have been exposed to corticosteroids.[17]

Women with diabetes have been specifically excluded from the majority of trials investigating antenatal corticosteroids, and hence, we have no reliable data to inform practice for these women whose babies are at the highest risk of respiratory morbidity. Despite a total lack of evidence from randomised trials regarding the effectiveness and safety of antenatal corticosteroids for women with diabetes having an elective CS beyond 35 weeks' gestation, our preliminary data demonstrate that corticosteroids are often being administered in this situation in Australia.

Given the rising rates of both diabetes in pregnancy and elective CS, there is an urgent need to provide the strongest level of evidence regarding the balance of benefits and risks of antenatal corticosteroids for women with diabetes, and their babies, born by elective CS. The PRECeDe trial is designed to provide this evidence.

Neonatal Respiratory Morbidity after Caesarean Section

Birth by elective CS, as opposed to vaginal birth or CS in labour, is associated with an increased risk of respiratory morbidity in the newborn,[18] which results in interventions such as assisted ventilation,[18] prolonged neonatal hospitalisation, separation from the mother, and delayed initiation of breast feeding.[10] All of these problems occur more frequently the lower the gestational age at birth[18] but even at 39 weeks gestation, the risk of respiratory morbidity is higher amongst those born by CS compared with those born vaginally (OR 1.9; 95% CI 1.2, 3.0), Figure 1.[3]

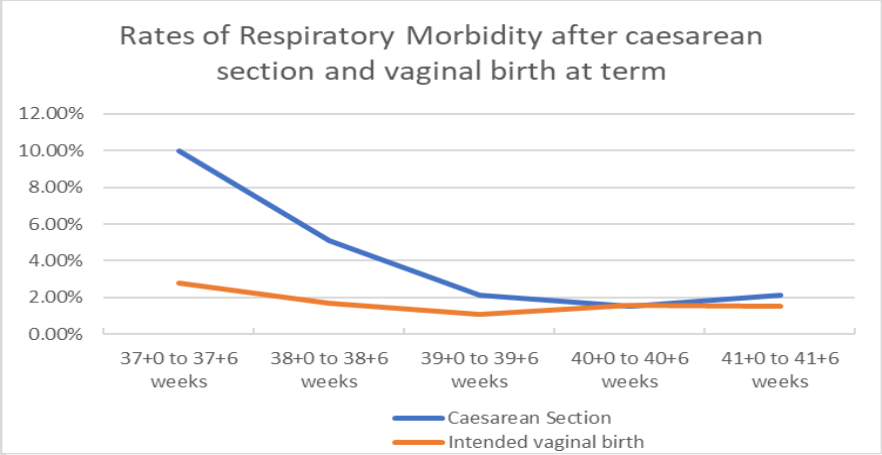


Figure 1: Increased rate of respiratory morbidity after caesarean section compared with intended vaginal birth (data adapted from Hansen AK et al [3]).

Neonatal Respiratory Morbidity in Infants of Women with Diabetes

Babies born to women with pre-gestational[7,9,19] or gestational[9,20] diabetes also have increased rates of neonatal respiratory morbidity even after adjusting for gestational age at birth, with infants whose mothers have Type 1 or Type 2 diabetes having a 2.5 fold[7] and 1.7 fold[9] increase in rates of neonatal respiratory distress, respectively. Likewise, a New Zealand study demonstrated that 50% of infants born to women with Type 2 Diabetes between 33 and 39 weeks experienced neonatal respiratory distress.[19] While the reasons for this are not fully understood, fetal hyperinsulinaemia, demonstrated by elevated umbilical cord c-peptide levels, is consistently reported in association with maternal gestational[21] and pre-gestational diabetes.[22] Several studies have suggested that this fetal hyperglycaemia and hyperinsulinaemia leads to a delay in maturation of the surfactant producing Type-II alveolar cells in the lungs of infants born to women with diabetes.[23-25] In addition, fetal hyperinsulinaemia is thought to mediate the fetal cardiac hypertrophy which is often observed during pregnancies complicated by diabetes,[26] and can contribute to left ventricular outflow obstruction, poor cardiac output and congestive cardiac failure after birth; a combination that also contributes to neonatal respiratory distress.[26] Women with diabetes have significantly greater rates of pregnancy complications including increased rates of stillbirth and pre-eclampsia,[9] so birth is frequently recommended prior to 39 weeks and is often required much earlier in the presence of pregnancy complications.[27,28] Earlier birth potentially compounds the risks of respiratory morbidity in these infants.

Neonatal Hypoglycaemia

Neonatal hypoglycaemia is commonly defined as a blood glucose concentration below 2.6 mmol/litre.[29] There is a well-established relationship between symptomatic neonatal hypoglycaemia and neonatal seizures,[30] brain injuries detectable with MRI, and poor neurological outcomes.[31] Even transient and mild hypoglycaemia that responds to treatment may still be associated with poorer neurocognitive[32] outcomes, and poorer academic performance at school age.[33]

Fifty percent of infants born to women with diabetes during the late preterm and term period develop neonatal hypoglycaemia[34] and infants of women with Type 1 diabetes have a 10-fold higher rate of neonatal hypoglycaemia compared with infants of women who do not have diabetes. Standard practice is therefore to specifically monitor neonatal blood glucose concentrations in infants born to women with diabetes, and institute early interventions to prevent and treat this problem, including early enteral feeding (breast milk or infant formula), oral dextrose gel, intravenous dextrose, or parenteral glucagon.[29] Admission to the neonatal nursery is common, separating mother and baby, and further reduces the chances of successful breast-feeding.

Antenatal Corticosteroids

Evidence from 26 studies which included 4469 women and 4853 infants summarised in the New Zealand and Australian Guideline on Antenatal Corticosteroids demonstrated significant reductions in the rates of respiratory distress in infants born prior to 34^{+6} weeks who received antenatal corticosteroids.[35] **However, only 5 of these trials included women with diabetes, so the total number of women with diabetes and their infants contributing data to inform management in this systematic review was just 45 and 51, respectively.[35]** Likewise, the majority of studies investigating the role of antenatal corticosteroids in preventing neonatal respiratory morbidity prior to elective CS either at term or during the late preterm period

excluded women with diabetes.[2,36] Only a single study investigating the role of antenatal corticosteroids during the late preterm period included a substantial number of women with gestational diabetes but excluded those with pre-gestational diabetes or gestational diabetes requiring pharmacologic treatment (Metformin or Insulin). However this subgroup of women with gestational diabetes was too small (n=306, representing 10.8% of the cohort) to have adequate power to address the question regarding the efficacy of antenatal corticosteroids in this specific population.[16]

A Cochrane systematic review summarising the four RCTs[2,36-38] that specifically investigated the efficacy of corticosteroids administered prior to elective CS birth after 37 weeks[1] demonstrated a statistically significant reduction in the overall rate of respiratory distress (risk ratio [RR] 0.48, 95% CI 0.27, 0.87; 3817 infants), transient tachypnoea (RR 0.43, 95% CI 0.29, 0.65; 3821 infants, Figure 2) or admission to the special care nursery for repiratory morbidity (RR 0.45, 95% CI 0.22, 0.90; 942 infants) in infants who were exposed to antenatal corticosteroids.[1] However, the quality of evidence, as assessed using GRADE, was low for the outcomes of RDS, TTN, and admission to the neonatal nursery for respiratory morbidity, indicating that the true effects could be substantially different from the reported estimates. Furthermore, significant methodological concerns have been raised about these trials which have now resulted in the retraction of the largest of these trials.[2,4,15] Only one of these four trials was placebo controlled,[2] (but as noted, this publication has now been retracted[39]) and only the ASTECS trial (Antenatal Steroids for Term Caesarean Section) included a small number of women with diabetes (10/942); insufficient to evaluate the efficacy of this intervention in infants born to women with diabetes.[37]. Importantly, the subsequent update of this Cochrane systematic review has now included just a single trial (ASTECS)[37] with a further 12 studies categorized as "awaiting classification" because they did not fulfil the Cochrane "trustworthiness criteria".[40]

No randomised trials have specifically investigated the effects of antenatal corticosteroids in women with diabetes before elective CS at late preterm or term gestations.

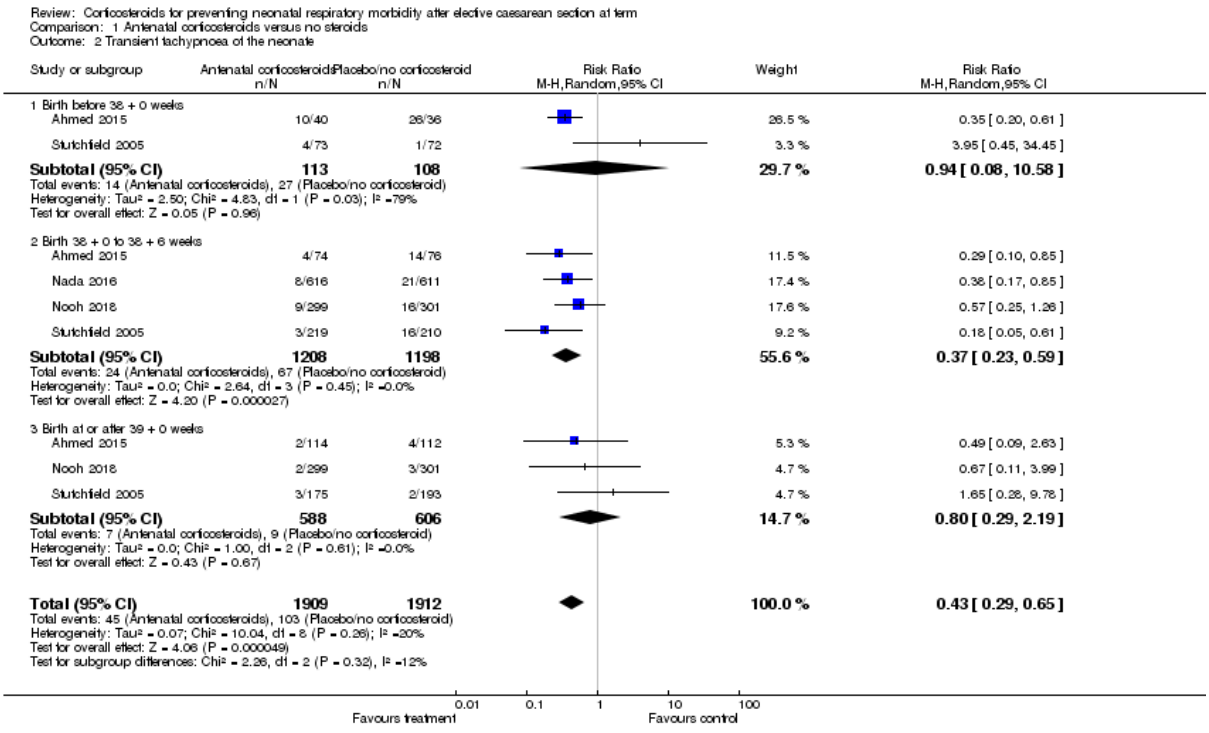


Figure 2: Reduction in the incidence of transient tachypnoea of the newborn following corticosteroid administration prior to elective CS.[1]. Note that the trial by Nada et al (2016)[2] has now been retracted.[4]

Effects of Antenatal Corticosteroids on blood glucose

Antenatal corticosteroids contribute to transient maternal hyperglycaemia,[41] and glucose is readily transferred across the placenta leading to fetal hyperglycaemia, with corresponding fetal hyperinsulinaemia. Thus, the maternal and fetal hyperglycaemia observed following administration of antenatal corticosteroids might exacerbate neonatal hypoglycaemia after birth.

Few studies have specifically reported neonatal hypoglycaemia following antenatal corticosteroid administration. However, Gyamfi-Bannerman et al reported a significant increase in the rate of neonatal hypoglycaemia following exposure to antenatal corticosteroids in infants at risk of birth between 34^{+0} to 36^{+6} weeks (OR 1.60, 95% CI 1.37 – 1.87, p<0.001), an unexpected finding.[16] Although this study did include some women with gestational diabetes who did not require pharmacological treatment, it is not clear whether hypoglycaemia was seen more frequently in this subgroup.

Long Term Consequences of Antenatal Corticosteroids

While the sparse medium and long term data regarding cardiometabolic health in children exposed to antenatal corticosteroids are generally reassuring, the majority of these data relate to administration of antenatal corticosteroids at early or moderate preterm gestations, rather than late preterm or term administration.[42-45] There are no data on the long term cardiometabolic outcomes of children born to women with diabetes who received antenatal corticosteroids at either preterm or term gestations. Such children may carry additional risk factors for cardiometabolic disease by virtue of the intrauterine exposure to maternal hyperglycaemia,[43,46] such that the additional exposure to a course of antenatal corticosteroids may further exaggerate cardiac risk factors or metabolic dysfunction. Indeed, the 30-year follow-up of children in the original trial of antenatal corticosteroids by Liggins in New Zealand suggested that adults who were exposed *in utero* to antenatal betamethasone were more likely to have increased insulin resistance at 30 years of age.[46]

Stutchfield et al reported on the behavioural and educational outcomes of a subset of school aged children (aged 8-15) who were involved in the ASTECS trial and showed no statistically significant differences in a range of parental reported indices of child behavioural and emotional health.[47] However, children exposed to antenatal betamethasone were more likely to be in the lowest quartile of academic ability based on a school assessment. These data must be interpreted with caution due to the low response rate for the overall follow-up study (only 43% of the original cohort of 942). Even fewer were involved in the school-aged assessment (37%). Furthermore, the ASTECS trial was designed as an open label trial and thus there was the potential for bias. Nevertheless, these data highlight the need for further follow-up of children from well conducted, randomised, placebo-controlled trials. Additional concerns have been raised from a large Finnish cohort study (n=670,097) demonstrating increased mental and behavioural issues in children exposed to antenatal corticosteroids born at term (8.9% in exposed children, 6.3% in unexposed children; hazard ratio (HR) 1.47 (95% CI 1.36, 1.60) p<0.001).[17] However, in this registry-based cohort study, the majority of these infants were exposed earlier in pregnancy due to a perceived risk of preterm birth, and not within the seven days prior to birth. Although the authors attempted to adjust for the huge range of confounders in this observational cohort study, it is possible that the steroid

exposed children represent a very different cohort to the unexposed group and that any differences in the childhood outcomes reflect the adverse pregnancy events in the corticosteroid exposed group rather than necessarily a direct effect of corticosteroids.[17] Importantly, there was no significant increase in the rate of severe or profound intellectual disability (HR 1.17; 95% CI 0.37 to 3.69) or even the rates of mild, moderate or unspecified intellectual disability (HR 0.96; 95% CI 0.64 to 1.42) in those exposed to corticosteroids but who were subsequently born at term. The increase in the primary outcome was driven predominantly by an increase in the rates of attention deficit hyperactivity disorder (HR 1.33, 95% CI 1.06 to 1.65, p=0.01)), "Other" behavioural and emotional disorders (HR 1.44, 95% CI 1.19 to 1.73, p<0.001), and sleep disorders HR 1.79 (1.31 to 2.44, p<0.001).[17]

As the fetal brain undergoes significant growth and maturation after 34 weeks,[48] and may be particularly susceptible to the effects of antenatal corticosteroids,[49] it is essential that neurological effects of antenatal corticosteroids are assessed, and that their overall safety and efficacy in women with diabetes are firmly established before they can be recommended for routine clinical practice.

Preliminary Studies

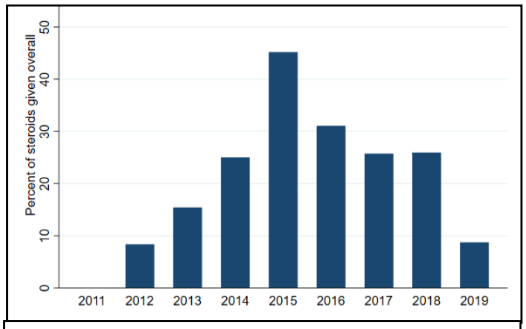


Figure 3: Percentage of women with pre-gestational diabetes receiving antenatal corticosteroids prior to elective CS at WH and RWH (n=306)

We studied the outcomes of infants born by elective CS between 36^{+0} weeks and 38^{+6} weeks to women with pre-gestational (Type 1 and Type 2) diabetes at Western Health (WH) and The Royal Women's Hospital (RWH) in Melbourne between 1/1/2011 to – 31/12/2019. Over this time we observed an initial increasing frequency of antenatal corticosteroid use within 7 days prior to elective CS peaking at 45% in 2015 followed by a significant decline (Figure 3) – likely coinciding with the publication of the Australian and New Zealand guidelines[35] in 2015. Findings from this retrospective, non-randomised, observational study are limited and did not demonstrate any statistically significant differences in outcomes amongst those exposed to antenatal corticosteroids compared with those who were not exposed (Table 1); however, more infants required IV therapy to treat neonatal hypoglycaemia.

Table 1: Associations between antenatal corticosteroid (ACS) administration and selected neonatal outcomes for babies born to women with pre-gestational diabetes (n = 306).

Outcome	ACS n=65	No ACS n=241	Odds ratio (95% CI)	p-value
Respiratory morbidity requiring support	5 (8%)	22 (9%)	0.83 (0.30, 2.28)	0.72
Admission to neonatal nursery	35 (54%)	106 (44%)	1.49 (0.86, 2.57)	0.16
Hypoglycaemia requiring IV therapy	31 (48%)	84 (35%)	1.70 (0.98, 2.97)	0.06

In our second observational study at Western Health in women with gestational diabetes treated with insulin (n=226), the findings were similar, with no significant reduction in the rates of neonatal respiratory distress in infants whose mothers received corticosteroids (10.2%) compared with those whose mothers did not (3.3%) - adjusted OR 1.77 (95% CI 0.41 - 7.65).[50] Of note, infants born to mothers with gestational diabetes had lower rates of RDS

than infants born to mothers with pre-gestational diabetes, consistent with the published literature.[7,8,20,51]

These preliminary studies informed the design of the PRECeDe Pilot Trial.

PRECeDe Pilot Trial

The PRECeDe Pilot Trial (ACTRN12619001475134) was a single-centred, double-blind, placebo-controlled trial designed to test the acceptability and feasibility of undertaking the PRECeDe Trial. The trial was conducted at Joan Kirner Women's & Children's at Sunshine Hospital, Western Health, Victoria between 1st June 2020 and 30th April 2022. Trial recruitment was slower than expected due to the challenges caused by the COVID pandemic which included cessation of research activity and redeployment of research staff. The planned sample size was 50 participants, however the trial was stopped early when funding was obtained for the multicentre trial. The early cessation allowed assessment of the feasibility to conduct a double blind placebo controlled trial. A total of 47 participants were recruited, representing 23.0% of eligible participants who were approached by a research midwife. There were no participant withdrawals following randomisation. A safety monitoring committee was convened and no serious adverse events were recorded. All processes including randomisation, treatment allocation, data collection, and postnatal follow-up were operationalised.

We assessed the ability for participants, clinicians and research staff to remain blinded to the treatment allocation[52] and found that while it was possible for some participants to guess their treatment allocation on the basis of the presence or absence of subsequent maternal hyperglycaemia, this was by no means the case for all participants (Table 2) and did not necessarily correlate with staff providing clinical care correctly guessing the treatment allocation. Both the midwife administering the study medication and the midwife collecting the research outcome data demonstrated the highest likelihood of accurately predicting the treatment allocation. In the former group, this was due to the recognition that even though the syringe was mostly masked with the trial identification label, the cloudy betamethasone suspension could still be distinguished from the clear saline solution in the trial syringes. The research midwives collecting the outcome data were able to correctly predict the treatment allocation on the basis of the presence or absence of maternal hyperglycaemia when the participant blood glucose monitoring logs were collected at the time of CS. While the blinding of participants was less optimal than we had hoped, the fact that clinicians providing postnatal care could remain blinded provides a justification to proceed with a double blinded study since it will be these clinicians who will make the decisions regarding patient care (maternal and neonatal) which form the basis of our primary and key secondary outcomes. We have also identified strategies to improve the syringe masking to ensure that staff administering the study medication would remain blinded. Preventing research midwives from collecting maternal blood sugar data by having participants upload these themselves (direct from their glucometer) will also help to maintain blinding of research personnel involved in the collection of outcome data.

As part of the pilot trial, a qualitative assessment of participant (n=13) and staff perspectives (n=10) of the trial was undertaken. All participants confirmed that they felt very well informed about the trial, found it highly acceptable, and an important topic to study. Likewise, interviews with staff indicated great confidence that the trial benefits outweighed the risks, and that this was an important trial to generate robust evidence to guide practice.

Table 2: Assessment of participant and staff blinding to treatment allocation

Group	Number of Trial Participants	Maximum number of staff who provided assessment for that participant	Fleiss's kappa	95% Confidence Interval
Participants	47	N/A	0.69	0.39 to 0.98
Doctor performing caesarean section	26	2	0.24	-0.22 to 0.71
Midwife or doctor receiving baby at birth	32	3	0.44	0.09 to 0.80
Endocrinologist with participant contact between treatment administration and birth	33	2	0.33	-0.01 to 0.67
Midwife or doctor caring for mother and / or baby in the ward	15	4	0.43	-0.10 to 0.96
Research midwife collecting outcome data	45	2	0.81	0.54 to 1.00
Midwife administering (or checking) trial medication	41	4	0.84	0.68 to 1.00

Fleiss's Kappa Interpretation: <0 Poor agreement between the predicted allocation and the true allocation; 0.01-0.20 Slight agreement; 0.21-0.40 Fair agreement; 0.41-0.60 Moderate agreement; 0.61-0.80 Substantial agreement; 0.81-1.00 Almost perfect agreement. N/A – not applicable

Current International Guidelines

International guidelines regarding antenatal corticosteroid use prior to elective CS vary considerably, and no guidelines provide specific recommendations for women with diabetes. The United Kingdom guidelines previously recommended that where elective birth by CS is required prior to 39 weeks, antenatal corticosteroids should be given,[53] although it is notable that this guideline has now been withdrawn from the Royal College of Obstetricians and Gynaecologists website, and been replaced by a guideline which does not include such a recommendation.[54] In contrast, the American College of Obstetricians and Gynecologists recommends antenatal corticosteroids for those at risk of birth prior to 36^{+6} weeks (regardless of mode of birth) although it remains cautious with respect to recommendations after 37 weeks' gestation.[55] The guideline specifically states that women with diabetes have not yet been studied during the late preterm period (34^{+0} to 36^{+6} weeks). The New Zealand and Australian guidelines recommend antenatal corticosteroids up to 34^{+6} weeks' gestation and specifically state that further research is required to assess the benefits and risks of antenatal corticosteroids beyond 35 weeks' gestation.[35] **A key research recommendation made by the authors of the New Zealand and Australian guideline is that further research in women with diabetes during pregnancy is urgently needed to assess the benefits and risks of antenatal corticosteroids beyond 35 weeks' gestation and particularly in women with diabetes during pregnancy.** The C*STEROID Trial (ACTRN12620000914965), funded by the Australian Medical Research Future Fund International Clinical Trials Collaboration and the Health Research Council of New Zealand is currently recruiting women without diabetes to address the specific question regarding the safety and efficacy of corticosteroids prior to elective CS in women without diabetes. The PRECeDe trial has been designed as an international, multicentred randomised trial to specifically address this research question in women with diabetes.

3.3 HYPOTHESIS

The overarching hypothesis is that administration of corticosteroids to pregnant women with either pre-gestational or gestational diabetes within 7 days prior to planned CS where CS is scheduled between 35^{+0} weeks and 39^{+6} gestation will reduce the incidence and severity of neonatal respiratory morbidity without adverse short-term (within the first 6 weeks) consequences for the mother or baby.

Specifically, we hypothesise that administration of corticosteroids to women with pre-gestational or gestational diabetes within 7 days prior to planned CS, where CS is scheduled between 35^{+0} weeks and 39^{+6} gestation, will:

1. reduce the incidence and severity of neonatal respiratory morbidity.

2. not increase the incidence of neonatal hypoglycaemia.

3. not increase the incidence of maternal morbidity (hyperglycaemia, chorioamnionitis, endometritis, or wound infection).

4. increase breast feeding rates at hospital discharge and 6 weeks post-partum.

5. reduce health care costs.

3.4 STUDY AIMS

Primary Aim: To measure the effect of maternal betamethasone administration (compared with normal saline placebo) on the incidence of neonatal respiratory morbidity requiring admission to the neonatal nursery and any form of respiratory support (e.g. intermittent positive pressure via an endotracheal tube, nasal continuous positive airway pressure (CPAP), Hi- or Lo-flow oxygen/air mixture, or increased ambient oxygen delivered into an incubator) for ≥60 minutes at any time following birth.

Secondary Aims:

1. To measure the effect of maternal betamethasone administration (compared with normal saline placebo) on a range of health outcomes for the mother and infant(s) (specific outcomes described in Section 4.3)
2. To undertake a cost effectiveness analysis of the intervention
3. To establish and maintain a cohort of sufficient size to undertake future longer term studies to evaluate childhood health and neurocognitive outcomes (these studies will be the subject of future applications)

4. OUTCOME MEASURES

Primary outcome: Respiratory morbidity, defined as requiring admission to the neonatal nursery and any form of respiratory support (e.g. intermittent positive pressure via an endotracheal tube, nasal continuous positive airway pressure (CPAP), Hi- or Lo-flow oxygen/air mixture, or increased ambient oxygen delivered into an incubator) for ≥60 minutes at any time following birth.

Secondary outcomes:

For the infant:

- hypoglycaemia defined as any blood glucose concentration <2.6 mmol/l;

- hypoglycaemia requiring treatment other than milk feeding (including dextrose gel, intravenous dextrose, glucagon);
- admission to a neonatal nursery and length of stay;
- severity of respiratory distress (severe: any intubation/mechanical ventilation and/or need for surfactant therapy; moderate: respiratory support (sum of mechanical and non-invasive) required for >24 hours; mild: the remainder requiring respiratory support for ≥60 minutes but <24 hours). The maximum appropriate mean airway pressure [MAP] for those requiring mechanical ventilation or nasal CPAP, and maximum appropriate fractional inspired oxygen [FiO2] for those requiring any form of respiratory support will also be recorded. For those on HiFlo, the maximum appropriate flow rate will be recorded.
- need for, and duration of, all forms of respiratory support (including all forms of respiratory support described in the primary outcome);
- use of exogenous surfactant;
- pneumothorax or air leak requiring drainage;
- presence of x-ray features suggestive of hyaline membrane disease or transient tachypnoea of newborn (independently adjudicated by a neonatal radiologist blinded to treatment allocation) in a subset of babes who require chest x-ray as part of clinical care.

For the mother:

- requirement for additional insulin therapy after administration of study drug;
- requirement for hospital admission between randomisation and CS;
- highest blood glucose concentration recorded between randomisation and birth;
- maternal infection from the time of randomisation up until 6 weeks' postpartum including chorioamnionitis; maternal pyrexia ≥38°C; wound infection requiring antibiotic or surgical /radiological (e.g. ultrasound-guided drainage) treatment;
- maternal reported side effects of the study drug;
- maternal mental health assessed using the Edinburgh Postnatal Depression scale (EPDS);[56,57]
- maternal general health prior to randomisation and at 6 weeks post partum assessed using the SF12[58] and AQoL8D.[59]
- breast feeding rates at hospital discharge and 6 weeks' post-partum.

Assessment of blinding: We will assess the ability to blind participants, clinicians and research staff to the treatment allocation in a subset of participants. This information will be used in interim analyses (if required) and will be collected and reported to ensure transparency regarding the conduct of the trial.

Health economics: We will assess the economic costs and benefits of this intervention at 6 weeks post partum and again at 2 years post partum under the supervision of AI Dalziel, who is a health economist. This will involve estimating the costs of administering the intervention compared with not administering the intervention. The hospital costs associated with each infant's birth admission will be obtained from administrative records and will reflect factors such as length of stay and admission to the neonatal nursery. Incremental cost effectiveness will be presented as a cost per case of respiratory morbidity avoided, a cost per case of respiratory support avoided and a cost per neonatal nursery admission avoided for the intervention group compared with the placebo group. Extensive one way and probabilistic sensitivity analyses will be conducted.

STUDY DESIGN

5.1 STUDY TYPE & DESIGN & SCHEDULE

The PRECeDe Randomised Trial is an international muticentre, randomised, triple blind, placebo controlled trial (Figure 4).

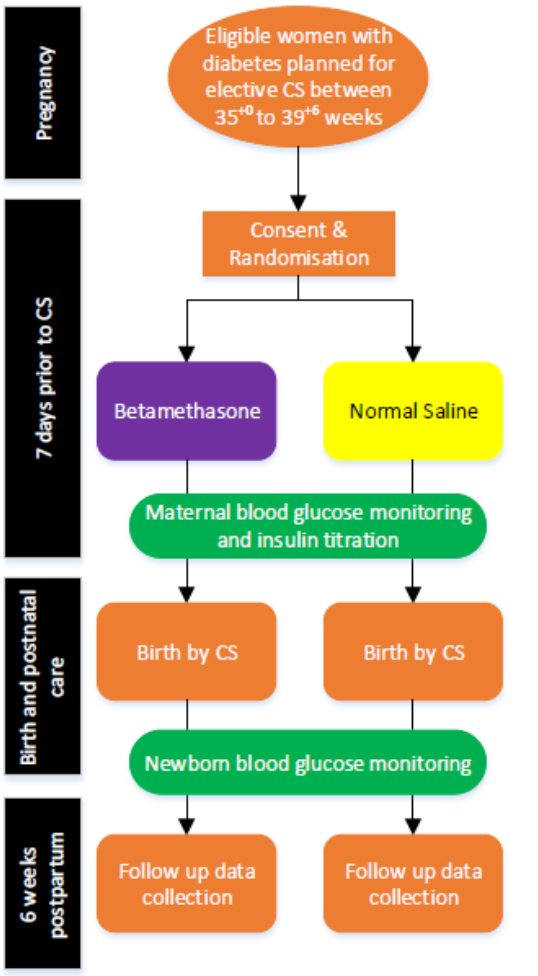


Figure 4: Trial Flow Diagram

Trial setting: The trial will be conducted in maternity units throughout Australia and New Zealand

Trial entry: Women will be identified and counselled by trained research midwives. Written consent will be obtained. In accordance with the CONSORT statement[60] we will collect data regarding the number of eligible participants, the number approached, and the number of participants who decline to take part in the trial via a waiver of consent to collect deidentified data regarding potentially eligible participants.

Randomisation: Eligible, consenting women will be randomised using a computer generated random number sequence. The randomisation schedule, using a 1:1 randomisation and variable block size will be prepared in advance.
Randomisation will be stratified by:

- Type of diabetes (Type 1 diabetes, Type 2 Diabetes, Gestational Diabetes)
- Gestation at delivery (35^{+0} to 36^{+6} and 37^{+0} to 38^{+6} weeks, 39^{+0} to 39^{+6} weeks)
- Recruiting site

Randomisation can only take place within 7 days prior to planned elective CS and at least 24 hours prior to planned elective CS to allow two doses of betamethasone to be administered prior to birth. Randomisation can occur within the week prior to 35^{+0} weeks gestation as long as the planned CS is scheduled after 35^{+0} weeks gestation.

Treatment Allocation: Assignment is to either the 'betamethasone group' or the 'placebo group'. A study number will be allocated to the participant that corresponds to the relevant trial treatment pack, each of which look identical and contain two masked syringes each containing either 11.4 mg of Celestone Chrondose in 2 ml (betamethasone 11.4 mg, as betamethasone sodium phosphate and betamethasone acetate) or placebo (normal saline 2 ml), both of which will be supplied and packaged by Baxter Healthcare Corporation who have confirmed stability testing for both the active drug and placebo for 180 days. Syringes will be masked with red tape to ensure that the volume of contents can be assessed but the betamethasone suspension will not be distinguished from the clear solution of the placebo. The syringes will be packaged with the appropriate randomisation number by Zeullig Pharma. All drugs will be prescribed by a medical practitioner as "Betamethasone 11.4mg in 2 ml, x2 doses or Normal Saline Placebo 2 ml, x 2 doses" and dispensed by Pharmacy staff at the recruiting site according to the allocated randomisation number.

Treatment schedules: Women in both treatment groups will be given the contents of one of their allocated syringes intramuscularly at least 24 hours prior to the planned CS. The second injection will be retained at the site and administered 24 hours (± 4 hours) later. Researchers, participants and staff will be blinded to the treatment allocation. If birth is required less than 24 hours after the first injection (for example, if the CS time must be brought forward due to maternal or fetal issues (eg spontaneous onset of labour), the second injection will be withheld. The reasons for not administering the second injection will be recorded on the CRF. The second injection should not be given earlier than 20 hours after the first injection. Failure to administer the second injection does not constitute withdrawal from the trial. There is no minimum amount of time required between the second injection and the CS.

If the CSis delayed beyond 7 days following administration of the two injections, repeat study medication (or antenatal corticosteroids) should not be administered.

Standard Care: Care for both groups will otherwise be according to standard practice for women with diabetes and their infants.

Monitoring of maternal blood sugars and treatment of maternal hyperglycaemia

All participants will be instructed to monitor their blood glucose using a capillary blood glucose monitor prior to every meal and 2 hours following meals for 72 hours after the first injection. Participants will be asked to record all blood glucose readings via REDcap with the link provided at the time of randomisation.Women who normally use continuous glucose monitoring or flash glucose monitoring should be advised to use capillary blood glucose monitoring according to the above schedule during this time period in addition to their continuous or flash blood glucose monitor. All participants will be provided with a site specific information sheet which will provide information about target blood sugars and what to do in the event of hypoglycaemia or hyperglycaemia. Women who experience hyperglycaemia will be advised to contact

the relevant staff at the participating site for advice regarding insulin titration. Maternal hyperglycaemia will be managed in accordance with local protocols with the aim being to ensure euglycaemia as much as possible. Staff who provide advice regarding the management of hyperglycaemia will be encouraged not to disclose whether they suspect the participant receive bethamethasone or placebo. Guidance regarding insulin management is provided in the PRECeDe Insulin Management Guideline (see Appendix 2) however relevant staff at each site will be responsible for individualising the care.

While, there is no requirement for women who are otherwise well to be admitted during the period between randomisation and the CS, individual sites may choose to arrange routine admission for close surveillance if that is their usual practice. Admission for close surveillance is recommended in the event of significant maternal hyperglycaemia or hypoglycaemia.

Monitoring of neonatal blood glucose and treatment of neonatal hypoglycaemia
Neonatal care for all infants will be in accordance with local protocols for the management of infants born to women with diabetes. At a minimum, all infants will undergo blood glucose testing (preferably using a glucose oxidase method (eg i-STAT or blood gas analyser) within the first 2 hours of life and then every 3-4 hours until 3 consecutive blood glucose recordings >2.6mmol/L. Further management including the treatment of hypoglycaemia and the timing of subsequent blood glucose measurements will be determined according to the local site algorithms. Where a site does not have a local algorithm, we recommend that Australian sites follow the Safer Care Victoria algorithm (Appendix 3) and New Zealand sites follow the Auckland DHB algorithm (Appendix 4)

Concomitant Medications / Treatments: All concomitant medications received by both the mother following randomisation, and the infant following birth, up until the time of discharge home following birth will be recorded. There are no restrictions regarding concomitant medications except antenatal corticosteroids (which constitute an exclusion criterion if received at any time before randomisation).

Compliance: Compliance with the allocated treatment schedule will be recorded, however as analysis will be by intention to treat, non-compliance with the allocated treatment schedule (including failure to complete the two injections) will not be regarded as an indication for exclusion or withdrawal from the trial.

Assessment of Blinding: The ability to retain blinding will be assessed in a subset of the participants if required (see section 7.4 Trial Risks). The following participant staff groups will be asked to predict which group the participant was allocated to (Betamethasone or Placebo or uncertain).
and their reason for this

- Participants
- Any staff members providing care for the participant or her baby
- Research staff involved in collection of outcome data

Data Collection: Prior to discharge following birth, participants will be asked by the site research team to complete a questionnaire about any side effects following trial medication administration. This will include questions regarding a range of symptoms including pain at the site of injection, flushing, fatigue, nausea, headaches, visual changes, changes in fetal movement patterns, hyperglycaemia, hypoglycaemia and adjustments to insulin doses.

After discharge of the mother and baby from hospital after the birth, the health outcome data will be collected from the case records by the research midwife at the recruiting centre and entered into a purpose built REDCap database.

Women and their children will be followed up afterischarge from hospital with questionnaires regarding additional maternal morbidity (wound infections, mental health) and neonatal morbidity (respiratory illness, method of feeding, and feeding difficulties) completed at 6 weeks' postpartum. In addition we will collect health information via the standardised SF12, EPDS and the AQoL-8D. Women who score ≥ 13 on the EPDS will be contacted by the lead investigator / trial coordinator at the respective site to assess maternal well being and will be directed to appropriate resources according to local guidelines.

All data will be entered into a REDCap database stored on a secure password protected server at The University of Melbourne.

Childhood Follow-Up: We will seek permission for on-going contact at least annually with mothers and their infants as part of the consent process.This contact will take the form of an email message with an annual 'birthday card' sent to the email address as well as an SMS request to update participant contact details. Future childhood follow-up studies are planned and separate funding will be sought to undertake these studies. All future studies will require HREC approval.

Emergency Unblinding: Unblinding is unlikely to be required for management of a participant with an adverse event as the effect of antenatal corticosteroids is generally short lived. However, emergency unblinding will be possible and can be arranged by contacting the Trial Coordinator or Coordinating Principal Investigator.

STUDY TABLE

	Assessment / Procedure	Screening (after 32 weeks)	Randomisation (within 7 days of planned elective CS)	First dose of betamethasone or placebo	Second Dose of Betamethasone or placebo (24 hours after first dose)	Caesarean Section and Post birth visit / data collection	Discharge of mother and baby	6 week follow-up	Annual follow-up
Procedures	Informed Consent	X							
	Demographic Information Weight & Height Measurement		X						
	Administration of Betamethasone or placebo			X	X				
	Symptoms questionnaire					X		X	
	Completion of EPDS, SF12, AQuOL 8D		X					X	
	Collection of data about blood glucose measurements and insulin doses			X	X	X			
	Collection of birth and neonatal data					X	X		
	Collection of participant assessment of blinding (subset of participants)						X		
	Collection of staff assessment of blinding (subset of participants)						X		
	Collection of maternal and neonatal outcome data (including neonatal blood glucose)						X		
	Collection of Mothers and babies health, breastfeeding and wound infection data							X	
	Completion of postpartum questionnaires							X	

	Annual email birthday card and SMS request to confirm contact details								X

6. STUDY POPULATION

6.1 INCLUSION CRITERIA

Pregnant women with a singleton or twin pregnancy who have pre-gestational diabetes OR gestational diabetes.

AND

plan to give birth by elective CS between 35^{+0} and 39^{+6} weeks gestation (randomisation can occur within the week prior to 35^{+0}).

AND

The CS is scheduled between 24 hours and 7 days from the time of randomisation.

Pre-gestational diabetes is defined (for the purposes of this trial) as either Type 1 or Type 2 diabetes that was diagnosed prior to the start of the pregnancy (regardless of whether the patient received medication for the diabetes prior to the start of the pregnancy).

Gestational diabetes is defined in Australia as an abnormal pregnancy 75 g Oral glucose tolerance test according to the WHO criteria for gestational diabetes.[61] Gestational diabetes is defined in New Zealand according to the Ministry of Health.[62] Gestational diabetes may also be diagnosed in either country via the modified criteria for diagnosis of gestational diabetes during the COVID-19 pandemic recommended by Royal Australian New Zealand College of Obstetricians and Gynaecologists and Australasian Diabetes in Pregnancy Society.[63]

WHO criteria for diagnosis of gestational diabetes or diabetes in pregnancy[61] :

a) Gestational diabetes mellitus should be diagnosed at any time in pregnancy if one or more of the following criteria are met:

- fasting plasma glucose 5.1-6.9 mmol/l
- one hour plasma glucose ≥ 10.0 mmol/l following a standardised 75g oral glucose load
- two hour plasma glucose 8.5-11.0 mmol/l following a 75g oral glucose load

b) Diabetes mellitus in pregnancy should be diagnosed if one or more of the following criteria are met[61] (however for the purposes of this trial, these participants will be classified as gestational diabetes):

- fasting plasma glucose ≥ 7.0 mmol/l
- two hour plasma glucose ≥ 11.1 mmol/l following a 75g oral glucose load
- a random plasma glucose ≥ 11.1 mmol/l in the presence of diabetes symptoms

New Zealand Ministry of Health[62] criteria for gestational diabetes:

- fasting plasma glucose ≥ 5.5 mmol/L
- two hour post-prandial plasma glucose ≥ 9.0 mmol/L following a 75g oral glucose load

The modified criteria for diagnosis of gestational diabetes during the COVID-19 pandemic recommended by Royal Australian New Zealand College of Obstetricians and Gynaecologists and Australasian Diabetes in Pregnancy Society:[63]

- Early pregnancy: HbA1c ≥5.9% OR Random blood glucose (RBG) ≥9.0mmol/L
- 24 -28 weeks' gestation: Fasting plasma glucose ≥ 5.1 mmol/L (Fasting plasma glucose <4.7 excludes the diagnosis of gestational diabetes. A formal glucose tolerance test is recommended for women with a fasting plasma glucose between 4.7-5.1)

6.2 Exclusion Criteria

- Known major fetal anomaly or chromosomal anomaly
- Administration of intramuscular antenatal corticosteroids (for fetal lung maturity) at any time during the pregnancy prior to ransdomisation
- Maternal systemic fungal infection
- Maternal thrombocytopaenia with a platelet count below $80x10^9$ /litre
- Hypersensitivity to betamethasone sodium phosphate, betamethasone acetate, or other corticosteroids
- Other contraindications to corticosteroids
- Prior participation in the PRECeDe trial in a previous pregnancy (prior participation in the PRECeDe Pilot trial is NOT regarded as an exclusion from participation in the current trial

6.3 Consent

Women will be identified and counselled by trained research staff under the supervision of the Principal investigator at each site. A patient information and consent form will be provided. Written consent or e-consent via REDCap will be obtained.

We seek a waiver of consent to screen patients for eligibility and collect deidentified data regarding the number of eligible participants, the number approached, and the number of participants who decline to participate consistent with the recommendations in the CONSORT statement.[60]

7. Participant Safety and Withdrawal

7.1 Participant Risk Management and Safety

Risk One: Potential for the trial to increase the CS rate and risks related to CS.
Women will be planning to undergo an elective CS. The decision to perform a CS and the timing of that procedure is made prior to inclusion in the study and as such the risks of this procedure are separate to the risks related to this trial. All women will receive formal advice from a hospital medical officer to allow them to give informed consent to the CS.

Risk Two: Potential for Maternal Harm

At present, there is no definitive evidence of risks associated with antenatal corticosteroid use in the manner described in this protocol. Women will be informed of the potential side effects which include pain, swelling and bruising at the injection site and maternal hyperglycaemia. The risks of maternal hyperglycaemia will be mitigated by regular assessment of the maternal blood glucose. In addition, we will ensure that there are always staff available at each participating site 24 hours a day, 7 days a week to provide telephone advice regarding management of maternal hyperglycaemia if this occurs.

Risk Three: Potential for Neonatal Hypoglycaemia

Neonatal hypoglycaemia is common in infants born to women with diabetes. Consistent with recommended practice, all infants will undergo neonatal blood glucose monitoring and treatment of hypoglycaemia. Recent evidence suggests that the detection and treatment of hypoglycaemia is not associated with any additional risks compared with infants at risk of hypoglycaemia who do not develop hypoglycaemia.[64]

Risk Four: Potential for longer term harms

Concerns have been raised about possible longer-term effects of antenatal corticosteroids on childhood development, including possible effects on learning, behaviour and psychological health.[17] Raikonnen et al reported a modest increase in the overall risk of psychological disorders in those who were exposed to antenatal corticosteroids, however, it is important to note that in this cohort study, corticosteroids were generally prescribed to those deemed 'at risk' of preterm birth (rather than within 7 days prior to planned CS birth after 35^{+0} weeks) and the cortiocosteroid exposed group were more likely to have premature rupture of membranes (16.7% vs 2.7%), hypertensive disorders (10.3% vs 4.0%), and maternal psychiatric disorders (26.7% vs 18.4%), and those born after 37 weeks had a significantly lower mean birth weight than their non-exposed counterparts (2659 ± 950 g vs 3548 ± 496g) – factors which themselves are associated with increased risks of adverse neurocognitive outcome.[17] Thus, the strength of the association between corticosteroids and adverse psychological outcomes remains uncertain. Importantly, this study did not demonstrate any association between antenatal corticosteroids and moderate (RR 0.96, 95% CI 0.64, 1.42, p=0.55) or severe / profound (RR 1.17, 95% CI 0.37, 3.69, p=0.53) intellectual impairment amongst those infants exposed to corticosteroids prior to 35 weeks but who were then born at term (after 37 weeks).[17]

While the assessment of longer term neurocognitive outcomes is beyond the scope of this trial, we will maintain contact with the cohort to ensure that these outcomes can be formally evaluated within the context of this randomised trial.

7.2 HANDLING OF WITHDRAWALS

Participants who choose to withdraw from the study will be invited to continue to provide data for the study including birth and neonatal outcome data as well as participation in the postnatal surveys at 6 weeks. Should they decline to contribute any data to the study, they will have the option to either retain existing data in the database (data collected prior to the withdrawl) or have their data deleted from the database and they will be regarded as a complete withdrawal from the study.

7.3 REPLACEMENTS

To preserve the statistical power of this trial, replacements will be permitted equivalent to the number of participants who withdraw from the trial.

7.4 TRIAL RISKS

Trial Risk One: Potential for unblinding of participants and staff

We will collect data regarding whether participants, clinicians and research staff remain blinded to the treatment allocation for a subset of participants. These data will only be collected in the event of (i) slow recruitment (see Trial Risk 2) or (ii) projected budget shortfalls (see Trial Risk 3). Data will be analysed prior to completion of the trial to determine whether the trial should pivot to an open label trial (ie betamethasone would be prescribed on site for participants allocated to betamethasone and participants, clinicians and research staff would be aware of the treatment allocation). The decision to pivot to an open trial will be made by the Trial Steering Committee if the Kappa statistic for participants, postnatal clinicians or research staff is above 0.41 (indicating moderate agreement between the partcipant, clinician or research staff and the true treatment allocation). Regardless of the success of blinding in the perinatal period, children would be assessed for outcomes in later childhood by health professionals who are unaware of their treatment group allocation; it is the later childhood outcomes that will be critical in determing the balance between risks and benefits of ACS.

Trial Risk Two: Slow recruitment

Given the pace of change in obstetric and neonatal practice, it is important that this trial is completed in a timely manner – with recruitment to be completed within the 5 year time frame. We will review recruitment progress every 6 months to consider strategies to improve recruitment. Recruitment targets will be established by the Trial Steering Committee at the time of activation of the first recruiting site(s). If recruitment is less than 80% of the expected target at 2 consecutive timepoints, the trial steering committee will consider the need to analyse the blinding assessment data (described in Trial Risk One) to determine whether the trial should pivot to an open label trial to allow a greater number of sites to participate.

Trial Risk Three: Budget shortfalls

While the research team have considerable expertise in managing research budgets, the requirement to use external suppliers for supply and packaging of investigational product together with the significant increase in the costs associated with regulatory authorities and freight may adversely affect the budget. Where a budgetary shortfall is anticipated, the Trial Steering Committee may request analysis of data collected regarding the ability to maintain blinding to determine if pivoting to an open label trial might help to reduce the costs associated with the trial.

8. STATISTICAL METHODS

8.1 SAMPLE SIZE ESTIMATION & JUSTIFICATION

A sample size of 2200 mothers (1100 in each arm, with continuity correction and allowing for 3% drop-out) will have 90% power to detect a relative reduction of 50% (absolute reduction of 3%) in neonatal respiratory distress from 6% to 3% with two-sided alpha of 0.05. This sample size will provide over 80% statistical power to detect a clinically significant increase of 30% in the secondary outcome of neonatal hypoglycaemia requiring treatment other than feeding

from 16% (from our pilot data for gestational diabetes and pre-gestational diabetes) to 20.8%.[50,65]

We have used the following to inform our sample size:

- The effect size for the primary outcome of 50% reduction in rate of respiratory distress is based on the ASTECS study (RR 0.46, 95% CI 0.23 – 0.93),[37] and is consistent with the effect size observed in the meta-analysis of antenatal corticosteroids for late preterm and term infants (RR 0.74 95% CI 0.61 – 0.91 overall and RR 0.40, 95% CI 0.27 – 0.59 when the analysis is restricted to those delivering by planned CSafter 37 weeks).[66] We consider a 50% reduction in the rate of respiratory distress requiring intervention for ≥60 minutes to be clinically relevant and likely to result in significant cost savings by preventing admissions to the neonatal nursery.
- The baseline prevalence of respiratory morbidity in neonates born to mothers with pre-gestational and gestational diabetes is estimated at 6% based on our preliminary studies from Sunshine Hospital and The Royal Women's Hospital. We have allowed for the higher prevalence of respiratory morbidity in babies born to women with pre-gestational diabetes (9% - Table 1) than to women with gestational diabetes (3-10%), but the lower prevalence of pre-gestational diabetes than that of gestational diabetes. This prevalence of respiratory morbidity is consistent with that observed in the ASTECS trial[37] (baseline prevalence of respiratory distress of 5.1%) and in the meta-analysis of antenatal corticosteroids in late preterm and term infants (7.2% in controls).[66]

8.2 Statistical Methods To Be Undertaken

We will undertake descriptive statistical analysis reporting the proportion of women screened, eligible, approached, consented and refused as well as the time taken to complete study procedures.

Outcomes will be compared between the intervention and control groups using an intention-to-treat analysis. For all binary outcomes the magnitude of the between-group differences will be quantified by fitting a logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for the corresponding population OR, stratified by recruitment site, type of diabetes (Type 1 diabetes, Type 2 Diabetes, Gestational Diabetes), and gestation at planned elective CS (35^{+0} to 36^{+6} weeks, 37^{+0} to 38^{+6} and 39^{+0} to 39^{+6} weeks). Linear regression will be used for non-categorical outcomes. For infant outcomes models will be fitted using Generalised Estimating Equations to allow for non-independence of outcomes among twins from the same pregnancy.
Assessment of blinding will be undertaken using Kappa statistic to assess the correlation between the participant or staff members "guess" of the allocation and the true allocation.

8.3 Interim analyses

If recruitment falls below 80% of the expected recruitment rate after two consecutive 6 monthly assessments, we will undertake a detailed assessment of research staff at participating sites to understand barriers and facilitators to recruitment. We will also commence the collection of data regarding the ability to maintain blinding for a minimum of 6 months (or until a minimum of 100 participants if fewer than 100 participants have been recruited in 6 months) to undertake an analysis of the potential to maintain blinding. If the blinding of participants indicates that there is at least moderate agreement between the participants prediction of the allocation and their true allocation (Fleiss's Kappa statistic is above 0.41), the Trial steering committee will recommend reverting to an "Open label trial" where the use of placebo is abandoned and

participants will be allocated to either “Open Label Betamethasone” (ie the participant, research staff and clinical staff will be aware of the patients allocation) or “standard care” without the use of either betamethasone or a placebo. An open label trial will allow additional sites to participate and substantially reduce the cost and logistics of the supply of masked betamethasone and normal saline syringes.

There are no other planned interim analyses for this trial. In particular, there will be no interim analyses based on the primary outcome. The Data and Safety Monitoring Committees may recommend an interim analysis if concerns are raised about the safety or benefit to risk profile of the trial.

9. Supply and Accountability of Investigational Product

Stocks of investigational product will be purchased directly from Baxter Healthcare. Stability of the investigational product has been confirmed for 180 days. Zeullig Pharma, a third party GMP certified pharmaceutical distributor will be contracted to mask the syringes in such a way that the solution within the syringe is visible (to ensure the correct volume and absence of air bubbles) but prevents the identification of the betamethasone suspension. Study drugs will be prepared in tamper proof packaging for each participant with the appropriate labelling corresponding to the randomisation number. Sufficient stocks will be held at each site to ensure no disruption in the trial supply, however stock quantities will be kept low as the shelf life of this product is only 180 days.

9.1 Drug Accountability

Each participating site will maintain a record of drugs dispensed for each participant and subsequent returns (eg if only a single injection is administered). Each site will also maintain a record of receipt for all study treatments and records regarding disposal of unused stock, or stock that exceeds the approved stability expiry date.

10. Storage of Blood and Tissue Samples

No blood or tissue samples will be collected for this study

11. Data Security & Handling

11.1 Details of where records will be kept & How long they will be stored

All hard copy data will be stored at each site by the study investigators at each site. Individual sites will be responsible fro ensuring that all hard copy data are stored appropriately All electronic data will be securely stored in a password protected database on a secure password protected server.

All data will be retained for 25 years consistent with requirements for interventional studies in pregnancy

After 25 years all paper data will be destroyed by secure shredding. All electronic data will be deleted.

11.2 Confidentiality and Security

All participants will be allocated an individual study number. This study number will allow re-identification of patient research data. The code linking the participant identifying data with the study number will be securely stored separately to the main database. All hard copy data will be stored in a locked filing cabinet located on Level 3 of the Western Centre for Health Research Education building at Western Health which is accessible only to the study investigators. All electronic data will be securely stored in a password protected REDCap database held on a secure password protected server at The University of Melbourne. Each participating site will only have access to data from their own site. For the purposes of contacting participants for long term follow up, identifying data will be held in the central database to allow the coordinating centre to maintain follow up. Identifying data will be held in a sperate database which will be linked to the research database through a unique participant identification code.

We will use social media to raise awareness of the PRECeDe Trial. This will allow some participants to identify themselves if they wish to discuss their experience of participation in this trial.

11.3 Access to Data and Data Sharing

The Trial steering committee will have full access to the dataset and oversee analysis, interpretation and reporting of the final results. After 12 months following publication of the primary results of the trial, the de-identified data can be requested for use in future research provided that

- The proposed use of the data is consistent with the objectives of the PRECeDe trial;
- Researchers provided a methodologically sound research proposal;
- Appropriate data management plans are in place

12. SAFETY REPORTING

12.1 Definitions

ADVERSE EVENT (AE) is any untoward medical occurrence in a participant administered an investigational product (or placebo) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).
Adverse events include the following:

- All suspected adverse drug reactions
- All adverse events related to the investigational product– overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)

- Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

AEs are not required to be reported unless they meet SUSAR (see below) and/or Outcome criteria.

SERIOUS ADVERSE EVENT (SAE) is any serious untoward medical occurrence. In this trial, the following will be considered as serious adverse events:

- Maternal death
- Neonatal Death
- Fetal Death (stillbirth)
- Maternal admission to intensive care unit
- Maternal life threatening event
- Maternal ketoacidosis
- Maternal hypoglycaemia associated with seizures or loss of consciousness within the first 7 days following the birth
- Neonatal hypoglycaemia associated with seizures or loss of consciousness within the first 7 days following the birth
- Maternal persistent or significant disability or incapacity
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated (including unplanned admission of the mother prior to CS)
- Readmission of the mother or baby following discharge from hospital

NOTES:
(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.
(iii) Note that admission to hospital for birth is not regarded as an SAE. Admission to hospital for >24 hours prior to CS birth is not regarded as an SAE if this is standard practice for women with diabetes (including those who receive corticosteroids) at the site, however unplanned admission to hospital prior to birth, or readmission following discharge from hospital after birth will be regarded as an SAE.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that

- is related to the drug and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or
- is not listed at the specificity or severity that has been observed;or
- is not consistent with the risk information described in the Patient Information and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

An event is causally related if there is a reasonable possibility that the drug caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

12.2 REPORTING OF SUSARS

All SAE's and SUSARs will be reported to the Trial Safety Monitoring Committee within 3 days of becoming aware of them by using the appropriate CRF (CRF 10: SAE Reporting). The Trial Safety Monitoring Committee will commence investigation of the SAE / SUSAR within 7 days and provide a report to the HREC and Trial Steering Group within 21 days.

The following information will be recorded for each SAE / SUSAR and reported to the Safety Monitoring Committee**:**

- Event description
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity
- Attribution to study intervention
- Action taken with study intervention, including administration or withholding of the second dose, if applicable
- Outcome of SUSAR including end date if recovered

13. TRIAL COMMITTEES

13.1 TRIAL STEERING COMMITTEE (TSC)

The PRECeDe Trial Steering Committe will be chaired by A/Prof Joanne Said and will include Prof Lex Doyle, A/Prof Katie Groom, Prof Caroline Crowther, Dr Amalia Karahalios and A/Prof Chris Yates. Additional members will be coopted as necessary.

13.2 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee comprising an obstetrician, endocrinologist, neonatologist and biostatistician with established terms of reference will review the trial safety, efficacy and conduct. The Data Monitoring Committee will review any safety issues reported by the Safety Monitoring Committee and provide recommendations to the Trial Steering Committee regarding the need for early termination of the trial if there are significant concerns regarding the safety.

The specific responsibilities of the DMC are to:

- assess trial recruitment rates
- assess data quality, including completeness
- monitor losses to follow-up and withdrawals
- monitor compliance with the protocol by participants and investigators including assessment of protocol deviations
- review aggregate AEs and SAE's according to treatment allocation group
- review reports of the SMC regarding SAE's
- suggest additional data analyses
- advise on protocol modifications suggested by investigators or sponsors (eg, to inclusion criteria, trial endpoints, or sample size)
- monitor planned sample size assumptions
- monitor continuing appropriateness of patient information
- monitor compliance with previous DMC recommendations
- assess the impact and relevance of any new external evidence

There will not be any interim analyses for the PRECeDe Trial.
The DMC reports to the TSC. The TSC reports to the Melbourne Health Research Ethics Committee and the Trial Sponsor

13.3 SAFETY MONITORING COMMITTEE (SMC)

A Safety Monitoring Committee comprising an obstetrician, endocrinologist and neonatologist with established terms of reference will review all Serious Adverse Events

and Suspected Unexpected Serious Adverse Reactions. The Safety Monitoring Committee will report to the Trial Steering Committee.

The specific responsibilities of the SMC are to:

- Undertake a review of all Serious Adverse Events (SAEs) within 3 days of notification by the Trial Steering Committee
- To complete the review of a SAE and report to the Trial Steering Committee (TSC) within 21 days of receiving a report of an SAE.
- To determine for each SAE reported whether the trial intervention was likely to be a causative factor
- Provide advice and recommendations relating to safety issues from SAEs to the TSC
- Request additional safety data or analyses

The SMC reports to the TSC.

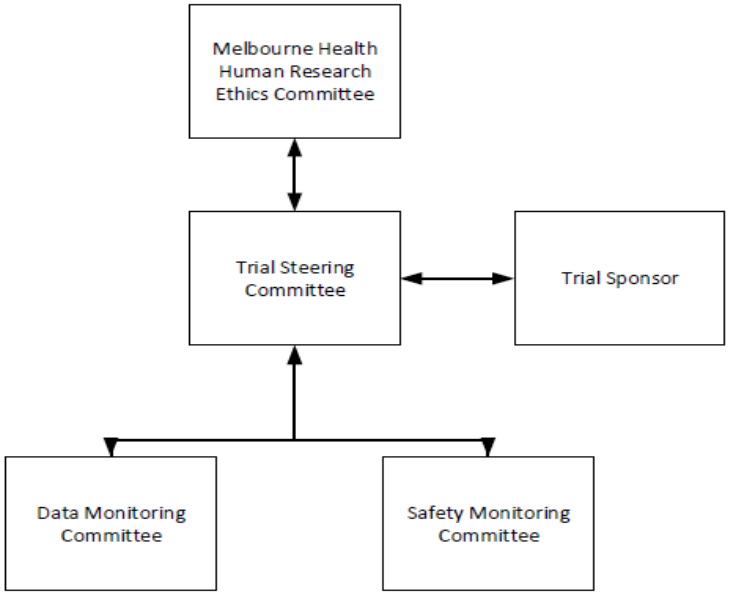


Figure 5: Relationship between Trial Committees

14. PUBLICATION POLICY

The Trial Steering Committee will appoint a Writing Committee to draft manuscript(s).

15. FUNDING

Funding for the PRECeDe Trial has been obtained from the National Health and Medical Research Council Clinical Trials and Cohort Studies Grant 2014750 (CIA Said)

16. APPENDIX

Appendix 1: List of Attachments included:

Document Name	Version Number	Date (e.g., 18 January 2012)
Patient Information Consent Form Master	2	4th August 2022
Patient Symptoms Questionnaire	1	11 May 2022
Participant Instructions Following Injections	2	8th August 2022
AQoL8D	12	23 March 2017
Edinburgh Postnatal Depression Score (EPDS)		
SF12	2	30 June 2002
Postnatal Questionnairre	1	8 August 2022
PRECeDe CRF 0	1	2 May 2022
PRECeDe CRF 1	1	2 May 2022
PRECeDe CRF 2	1	2 May 2022
PRECeDe CRF 3	1	2 May 2022
PRECeDe CRF 4	1	2 May 2022
PRECeDe CRF 5	1	2 May 2022
PRECeDe CRF 6	1	2 May 2022
PRECeDe CRF 7	1	2 May 2022
PRECeDe CRF 8	1	2 May 2022
PRECeDe CRF 9	1	2 May 2022
PRECeDe CRF 10	2	12 August 2022
PRECeDe CRF 11	1	2 May 2022
PRECeDe CRF 12	1	2 May 2022
PRECeDe Blood Sugar Diary Master	1	11 May 2022
PReCeDe Poster Master	1	11 May 2022

CS Weekly Screening Log	1	11 May 2022
PRECeDe Safety Monitoring Committee Terms of Reference	1	22 August 2022
PRECeDe Data Monitoring Committee Terms of Reference	1	22 August 2022

Appendix 2: Management of hyperglycaemia between study drug injection and elective caesarean section – Guidance for Staff providing insulin titration advice

Blood Glucose (BGL) monitoring:

- BGL monitoring should occur fasting, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner and 2 hours after dinner
- The target BGLs are ≤5.0 mmol/L fasting and <6.7 mmol/L 2 hours after meals or according to local hospital protocols
- Notify the designated staff if hypoglycaemia (BGL<3.5mmol/L) or hyperglycaemia with BGL >8 mmol/L

Hypoglycaemia

- In women with GDM, manage hypoglycaemia if BGL <3.5 mmol/L
- In women with pre-gestational type 1 or type 2 diabetes, manage hypoglycaemia if BGL <4.0
- If hypoglycaemia persists despite treatment, consider fetal well being assessment according to local hospital protocols.

Blood ketone level checks:

- Consider checking blood ketone levels if BGL >10.0 – especially in patients with Type 1 diabetes

Additional Insulin

In addition to the diabetes management regimen prior to administration of trial medication, consider supplemental sliding scale of short-acting subcutaneous insulin (e.g. Novorapid®) in the event of hyperglycaemia. Dose adjustments are at the discretion of clinical staff at the participating site and should take into account the participant's type of diabetes and diabetes management. Advice should be individualised with the aim being to ensure euglycaemia without disclosing whether the staff member suspects the participant received betamethasone or placebo.

- Participant should be advised to contact a nominated member of staff at the site (eg endocrinologist, obstetric physician, diabetes educator) if there are two results above the target BGLs of ≤5.0 mmol/L fasting or <6.7 mmol/L 2 hours after meals OR if there is a single result more than 8.0 mmol/L
- If pre-prandial blood glucose is between 8.1-10 mmol/L, 2 extra units of short-acting insulin should be administered.

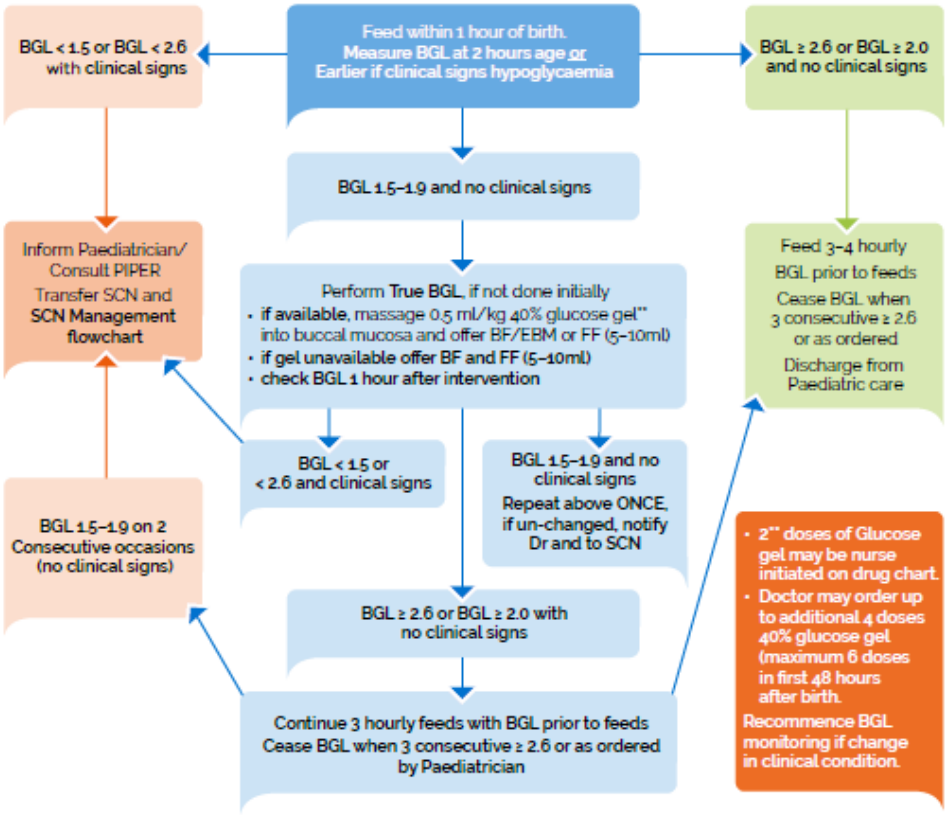
- If pre-prandial blood glucose is between 10.1-12 mmol/L, 4 extra units of short-acting insulin should be administered.
- If pre-prandial blood glucose is between 12.1-14 mmol/L, 6 extra units of short-acting insulin should be administered.
- If pre-prandial blood glucose is between 14.1-16, 8 extra units of short-acting insulin should be administered.
- If pre-prandial blood glucose is greater than 16, 10 extra units of short-acting insulin should be administered.

Appendix 3: Safer Care Victoria Algorithm for the Management of Infants at Risk of Hypoglycaemia

Safer Care Victoria | Maternity and Newborn Network

Postnatal Ward

Management of Infants at risk of Hypoglycaemia



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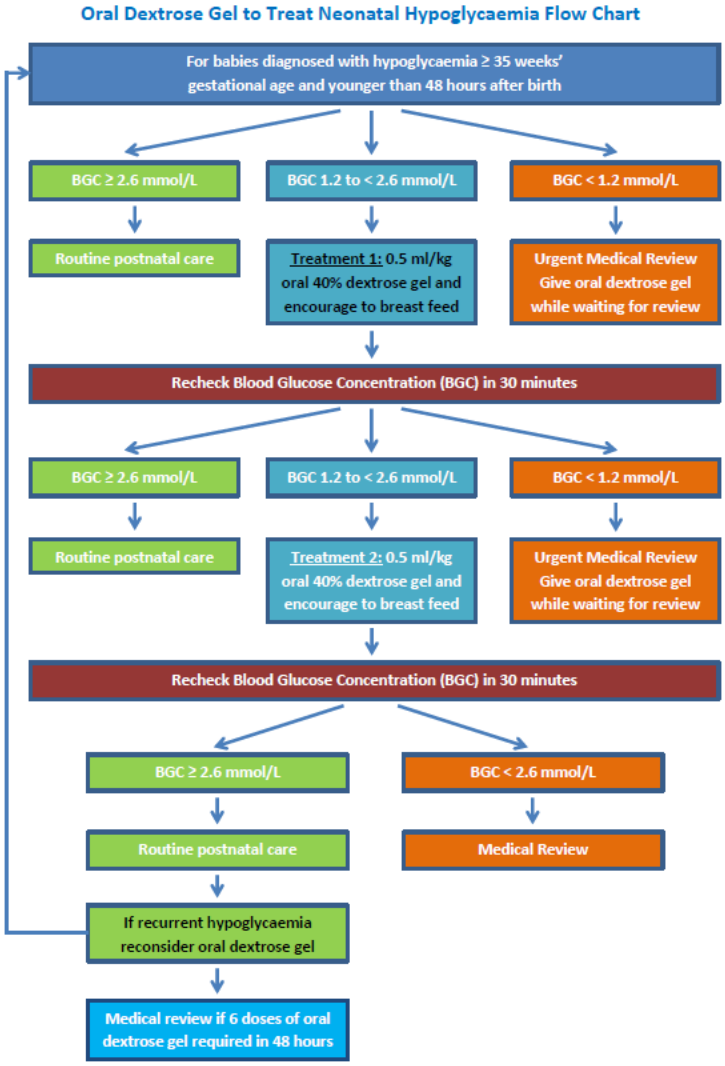
VICTORIA State Government

Appendix 4: New Zealand Clinical Practice Guideline regarding the management of infants at risk of hypoglycaemia

Continue monitoring blood glucose concentrations until 3 consecutive blood glucose concentrations are ≥2.6mM
Downloaded from: https://starship.org.nz/guidelines/hypoglycaemia-in-the-neonate/



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