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RidStress 2 randomised controlled trial protocol: an Australian phase III clinical trial of intrapartum sildenafil citrate or placebo to reduce emergency caesarean birth for fetal distress in women with small or suboptimally grown infants at term (≥37 weeks)

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ABSTRACT

Introduction Small for gestational age (SGA) infants are at increased risk of fetal distress in labour requiring emergency operative birth (by caesarean section (CS), vacuum or forceps). We have previously shown that maternal oral sildenafil citrate (SC) in labour halves the need for operative birth for suspected fetal distress in women with appropriately grown term infants.

Methods and analysis RidStress 2 is a phase III randomised, double-blinded, placebo-controlled trial of 660 women with an SGA or suboptimally grown fetus (estimated fetal weight or abdominal circumference<10th centile for gestational age) planning a vaginal birth at term. The trial will determine whether oral intrapartum SC (50 mg eight hourly) reduces the relative risk of emergency CS for fetal distress compared with placebo. The primary outcome is CS for fetal distress, and the secondary outcomes are any operative birth for fetal distress, cost-effectiveness of SC treatment and 2-year childhood neurodevelopmental outcomes. To detect a 33% reduction in the primary outcome from 30% to 20% for an alpha of 0.05 and power of 80% with 10% dropout, requires approximately 660 women (330 in each arm). This sample size will also yield >90% power to detect a similar reduction for the secondary outcome of any operative birth (CS or instrumental vaginal birth) for fetal distress.

Ethics and dissemination Ethics approval was granted by the Mater Misericordiae Limited Human Research Ethics Committee (EC00332) on 11 September 2020. We plan to disseminate the results of this randomised controlled trial through presentations at scientific meetings and peer-reviewed journals, adhering to all relevant reporting guidelines.

Trial registration number RidStress 2 is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000354886, 29/03/2021) and the Therapeutic Goods Association of Australia (date registered: 16 March 2021).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ RidStress 2 will prospectively determine if intrapartum maternal oral sildenafil citrate reduces the risk of emergency operative birth for fetal distress in small for gestational age infants.
⇒ By assessing neurodevelopmental outcomes at 2 years of age in offspring, longer-term benefits or harm can be ascertained.
⇒ For efficient recruitment, RidStress 2 recruitment will be limited to larger tertiary centres in Queensland. This may limit generalisability beyond the tertiary setting.

BACKGROUND AND RATIONALE

Small for gestational age (SGA) infants (birthweight<10th centile for gestational age) and those with fetal growth restriction (FGR) are at greater risk of developing fetal distress in labour and requiring operative birth,[1–3] compared with their appropriately grown counterparts. Due to underlying placental dysfunction (which limits nutrient and oxygen transfer),[4 5] this cohort poorly tolerates the intermittent hypoxic episodes generated by uterine contractions during labour.[6] They are thus unable to substantially use anaerobic metabolism to generate energy because of reduced cardiac and hepatic glycogen stores.[7–10 10] The hypoxic challenge of labour rapidly diminishes these stores, leading to impaired myocardial function,[11] cerebral hypoperfusion[12] and consequent fetal distress[13] and acidosis,[12] necessitating

emergency caesarean section (CS) or instrumental vaginal birth (IVB).[2 14 15]

Intrapartum fetal distress is the primary indication for ~23% of CS births in Australia.[16] Both emergency CS and IVB are associated with significant maternal and neonatal morbidity[17–19] as well as implications for future pregnancies.[20–22] Effective strategies to reduce emergency CS and IVB rates related to intrapartum fetal distress are thus urgently needed and are important research priorities.[18 23]

Sildenafil citrate (SC) is a phosphodiesterase-5 inhibitor (PDE-5) and potent vasodilator, which prevents intracellular degradation of cyclic guanosine monophosphate and increases bioavailability of nitric oxide.[24 25] PDE-5 is present in smooth muscle of blood vessels, including those of the uterus and placenta.[24 26] SC has been shown to improve fetoplacental blood flow in pregnancies complicated by FGR[27–29] and has a favourable safety profile in pregnancy.[30 31]

Our earlier phase II randomised controlled trial (RCT) (RidStress)[30] demonstrated that compared with placebo, intrapartum oral SC reduced emergency operative birth for fetal distress by 51% (RR 0.49, 95% CI 0.33 to 0.73, p=0.0004) and halved rates of pathological fetal heart rate patterns (15% vs 32%; RR 0.48, 95% CI 0.31 to 0.75, p=0.0009) for women in term labour. A subgroup analysis of women with infants weighing <10th centile for the study cohort demonstrated a non-significant reduction in operative birth (CS and IVB) for fetal distress (11.8% vs 38.5%; RR 0.31, 95% CI 0.07 to 1.33) and double the spontaneous vaginal birth rate (82.4% vs 38.5%; RR 2.14, 95% CI 1.04 to 4.41, p=0.02). We also demonstrated that women in the SC arm had a lower intrapartum decline in placental growth factor (PlGF) levels in labour, and the possible protective effect of SC was greatest in those with pretreatment PlGF levels of 85–400 pg/mL (p=0.004).[32] PlGF is a marker of placental function and has an important role in promoting angiogenesis and endothelial cell proliferation.[33 34]

The aim of this phase III RCT is to investigate if, compared with placebo, SC safely reduces emergency operative birth for fetal distress in women with SGA or suboptimally grown infants planning a vaginal birth at term. RidStress 2 will also contribute to an individual participant data prospective meta-analysis with considerably greater power to detect moderate benefits and harms.

Safely reducing CS births is an international research priority,[20 23] particularly in low-income and middle-income countries (LMICs), which might experience even greater obstetric and perinatal benefits. Although LMICs have very high rates of SGA infants,[35] they often lack the facilities for intrapartum monitoring and emergency operative birth, resulting in avoidable intrapartum stillbirths or neonatal deaths after birth asphyxia. The vast majority of all stillbirths occur in LMIC, with half occurring in labour.[17 35] SC is now off-patent, inexpensive, stable, easily administered orally with a favourable safety profile in about 1000 women so far.[31] If routine intrapartum SC safely reduces adverse birth outcomes and/or emergency operative birth and their long-term sequelae, it could improve maternal and neonatal outcomes of clinical care across a diverse range of healthcare settings and provide an important option for women attempting vaginal birth worldwide.

We hypothesised that women with an SGA infant may derive greater benefit from intrapartum SC therapy, resulting in lower rates of intrapartum fetal compromise and emergency operative birth for fetal distress.

AIMS AND OBJECTIVES

This study aims to test the hypotheses that up to three oral doses of 50 mg SC (vs placebo) is safe and will reduce the relative risk of emergency operative birth for fetal distress in women with an SGA or suboptimally grown fetus.

Our objective is to undertake a 4-year, phase III RCT (RidStress 2) of 660 women with suspected SGA or FGR planning a vaginal birth at term (*population*), to test if SC (*intervention*) safely reduces the relative risk of emergency CS for fetal distress by 33% (from 30% to 20%) (*primary outcome*) compared with placebo (*comparator*). An assessment of infant neurodevelopmental outcomes at 2 years will be undertaken, and a health economic analysis will be conducted.

Primary objective

To evaluate whether, compared with placebo, SC achieves a 33% reduction (from 30% to 20%) in the relative risk of emergency CS for fetal distress (primary outcome).

Secondary objectives

1. To evaluate whether, compared with placebo, SC reduces the relative risk of any operative birth (CS and IVB) for fetal distress by 33% (from 40% to 26%) and has similar perinatal and maternal outcomes.
2. To evaluate whether, compared with placebo, SC reduces rates of neurodevelopmental delay at 2 years of age.
3. To evaluate whether, compared with placebo, SC is cost-effective.
4. To evaluate whether prelabour maternal PlGF or soluble Fms-like tyrosine kinase-1 (sFlt-1), fetal biometry or fetoplacental Doppler assessment can stratify women who would benefit more from intrapartum SC therapy.

METHODS AND ANALYSIS

Trial design

RidStress 2 is a two-arm parallel, randomised (1:1), placebo-controlled, double-blind, multicentre, superiority trial of intrapartum SC versus placebo in 660 women with a suspected SGA or suboptimally grown fetus at term ($\geq 37^{+0}$ weeks' gestation).

Trial setting

RidStress 2 will be conducted at the Mater Mothers' Hospital, Royal Brisbane and Women's Hospital, Sunshine Coast University Hospital and Gold Coast University Hospital in Queensland, Australia. Recruitment to RidStress 2 began on 27 July 2021, and recruitment is planned to continue until 11 September 2025.

Patient and public involvement statement

We involved clinician and consumer groups when designing this trial.

Study population

Inclusion criteria:

1. Singleton pregnancy.
2. Planning a vaginal birth at term (>37 weeks' gestation).
3. Aged>18 years and able to give informed consent.
4. Pregnancy complicated by suspected SGA infant or late FGR.

SGA is defined as estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile for gestation based on ultrasound assessment.

FGR[36] is defined as EFW or AC <3rd centile or two out of three of the following:

1. EFW or AC <10th centile.
2. AC or EFW crossing centiles by>2 quartiles on growth charts (for the purposes of this trial, we defined this change over a minimum interval of 4 weeks).
3. Cerebroplacental ratio<5th centile or Umbilical Artery Pulsatility Index>95th centile for gestation.

Exclusion criteria:

1. Two or more previous CS births.
2. Previous classical CS.
3. Major fetal anomaly in this pregnancy.
4. Non-cephalic presentation.
5. Severe hepatic or renal impairment.
6. Participants who are taking any type of nitrate drug therapy or who use short-acting nitrate-containing medications during labour (such as sodium nitroprusside, bosentan, fosamprenavir and ritonavir combination, hepatic enzyme inhibitors CYP3A4 (including itraconazole, ketoconazole, ritonavir, cimetidine, erythromycin, saquinavir, darunavir), or hepatic enzyme substrates (CYP3A4), medications used to treat pulmonary arterial hypertension, and other phosphodiesterase type 5 inhibitors like riociguat), due to the risk of potentially life-threatening hypotension.

Screening, registration and randomisation

This is summarised in figure 1. Women will be screened for eligibility and approached by obstetric caregivers or research midwives to participate in the trial from 32 weeks' gestation onwards. A confidential record of women who were screened for eligibility, approached and consented will be kept at each study site. For women who decline participation, a reason will be recorded where given. The rights of women to decline participation without providing a reason will be respected.

Signed consent to enter the study will only be obtained by members of the study team after full explanation and adequate time for consideration of information detailed in the patient information and consent form (online supplemental appendix 1). Consent may be obtained in-person, over the phone or by email. All participants will be free to withdraw from the trial at any time without reason or prejudice of their ongoing care. Women will receive no financial incentive to participate in this study. Their participation will be documented in their obstetric record and alerts placed on the relevant electronic patient administration systems. An email will be sent to women following their registration providing contact details for the trial staff and a copy of their signed patient information and consent form. All women will receive routine obstetric care until the onset of spontaneous labour or induction of labour (IOL).

Women will also be invited to consent to participate in childhood neurodevelopmental follow-up. If they consent, contact details will be recorded and follow-up assessment will be performed as described below. If consent is declined or withdrawn before follow-up takes place (2 years corrected age), no further contact will take place.

Prior to IOL or spontaneous labour, 20 mL of blood will be collected for assay of soluble sFlt-1 and PlGF levels. Excess serum and plasma will be aliquoted and stored for future related research at Mater Research Institute, University of Queensland, for which separate ethical approvals will be obtained. This is outlined in the patient information and consent form.

Interventions

The study intervention is oral SC 50 mg, and the comparator will be an identical matching placebo. The trial medication will be given when participating women are admitted to the labour ward, either in spontaneous labour or for IOL (artificial rupture of membranes ± syntocinon infusion). Women will be given the study treatment by the attending midwife in the labour ward. Women will receive SC 50 mg or identical placebo orally every 8 hours until birth of the baby to a maximum of three doses. Participants who satisfy the below criteria will have their treatment ceased:

1. Acute severe maternal hypotension (<60/40 mm Hg × three episodes) sufficient to cause maternal and/or fetal compromise occurs.
2. The participant requests discontinuation from study.
3. The investigative team believes it is in the best interest of the participant on grounds of safety or side effect or tolerability that discontinuation takes place.

To monitor adherence to the trial intervention, the date and time of study drug administration will be recorded, unused investigational product will be returned to pharmacy, and accountability logs will be kept. An instruction sheet outlining trial processes will be provided to the attending midwife, and 24-hour phone support will be provided by the research team. Both the clinical and

	Study period									
	Enrolment		Post-allocation							Close-out
TIMEPOINT*	***>32 weeks gestation***	***>36 weeks gestation***	***Labour***	***Delivery of infant***	***7 day follow up***	***28 day follow up***	***6 month follow up***	***12 month follow up***	***18 month follow up***	***2 year follow up***
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Registration on Trial Database		X								
Allocation according to randomization schedule		X								
INTERVENTIONS:										
[Sildenafil 50mg capsule, orally, 8 hourly until delivery of infant or 3 doses]			X							
[Placebo]			X							
ASSESSMENTS:										
Maternal baseline variables		X								
Collection of maternal blood samples		X								
Maternal Obstetric Outcome Variables				X	X					
Neonatal Outcome Variables				X	X	X				
Collection of cord blood samples				X						
Placental histopathology				X						
Assessment of 28 day neonatal mortality						X				
Confirmation of Contact Details							X	X	X	
2 year neurodevelopmental assessment										X

Figure 1 Schedule of enrolment, interventions and assessments for RidStress 2.

research teams will collaborate to monitor adherence to trial processes.

Management of labour and puerperium

Management of labour will be in accordance with local protocols and guidelines. All women will have continuous electronic intrapartum fetal heart rate monitoring, with abnormalities classified according to Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines.[15] In the event of operative birth, the attending obstetrician will be asked to confirm the indication for operative birth and the role that fetal distress played in their decision-making.

Umbilical artery cord pH will be measured in all women after birth. Delayed cord clamping will always be facilitated. Where possible, 20 mL of cord blood will be collected for SC assays and storage for future research related to this study. The placenta will be sent for routine histopathological examination as per institutional guidelines. All biospecimens will be registered and stored at the Mater Research Institute in Brisbane, Australia.

All infants will also receive routine oxygen saturation screening 24–48 hours after birth (current standard practice in Australia). This test complements the newborn physical examination and is used to detect hypoxaemia in infants. Infants with oxygen saturation>95% are very unlikely to have major congenital heart or significant pulmonary disease (including persistent pulmonary hypertension of the newborn). Infants with oxygen saturations<95% will receive further assessment by the paediatric team and additional investigations will be performed as required.

Trial outcomes

Primary outcome

Emergency CS for fetal distress (defined contemporaneously as an abnormality in fetal heart rate pattern, fetal scalp lactate or pH).

Secondary outcomes

Any operative birth (CS or IVB) for fetal distress, health economic costs, 2-year childhood neurodevelopmental outcomes and correlation between maternal placental biomarkers, prelabour ultrasound variables.

Obstetric and maternal outcomes

Other indications for operative birth, spontaneous vaginal birth, postpartum haemorrhage (blood loss>1.5 L), blood transfusion, peripartum hysterectomy, uterine rupture, third and fourth degree tears, length of stay in hospital, intensive care unit admission.

Perinatal outcomes

Intrapartum stillbirth or neonatal death<28 days, Apgar≤4 at 5 min, severe acidosis (cord artery pH<7.0 or base excess < −12 mmol/L), neonatal encephalopathy, seizures, respiratory support>4 hour, neonatal intensive care unit (NICU) admission>48 hours, persistent pulmonary hypertension of the newborn or meconium aspiration syndrome.

Sample size

The incidence of the primary outcome is estimated at 30% based on data in a large recent RCT in term pregnancies[37] and local data from Mater Mother's Hospital. To detect a 33% reduction in the primary outcome from 30% to 20% for an alpha of 0.05 and 80% power with 10% dropout in each arm needs approximately 660 women (330 in each arm) (https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html). This sample size will also yield>90% power to detect a similar reduction for the secondary outcome of any operative birth (CS or IVB) for fetal distress.

Allocation and concealment of intervention

A computer-generated randomisation schedule with permuted block randomisation with randomly selected block sizes will be used. The block sizes and the randomisation schedule will be concealed to clinical staff, research staff and participants. Stratification will be performed by study site to ensure balance in treatment assignment across sites. The randomisation schedule was provided to the pharmaceutical manufacturer and identical trial medication kits containing either SC 50 mg or placebo were produced and numbered sequentially. Kits were then allocated sequentially to registered participants by the research staff.

Blinding

Participants, research staff and healthcare providers will remain blinded to intervention allocation. Assessments of all outcomes and data analysis will be performed in a blinded manner. If emergency unblinding is deemed in the best interest of the participant or their infant, authority to do so will be obtained from the principal investigator, trial statistician and pharmacist. Unblinding will only occur if knowledge of the allocated treatment group is essential for ongoing management of the patient or their infant. The need for unblinding should be very uncommon, as the study intervention is rarely associated with severe side effects.[31]

Data collection and management

All data collection will be recorded into electronic case report forms and stored in a secure online database (RedCap). Valid values, expected ranges and descriptions selected from a list will be specified in the electronic database to ensure data integrity. Baseline demographic and obstetric data will be entered into the RedCap database at the time of registration. Data for primary and secondary outcomes will be ascertained by reviewing the participants' medical records and cross-checked against details provided by the treating obstetrician. Adverse maternal and neonatal outcomes will be assessed by review of the participants' medical records at 7 days and at the 28-day follow-up. When the infant approaches 2 years, participants will be sent an electronic version of the Ages and Stages Questionnaire.[38] To promote retention

of trial participants until the time of neurodevelopmental follow-up, 6 monthly phone calls to participants will be made.

Data analysis plan

Primary and secondary outcome analyses will adhere to an intention-to-treat basis, so all women randomised are analysed in their allocated group, using generalised linear models (binary or normal). Intervention effect will be presented as relative risk or mean difference as appropriate, with 95% CIs. Two-tailed p value<0.05 will be considered statistically significant. Primary analyses will be unadjusted. Number needed to screen and treat to prevent one adverse primary outcome will be calculated. Where there are differences in the baseline characteristics between the two treatment groups that might be associated with outcomes, secondary adjusted analysis of the primary outcome will be carried out using multiple (log-binomial) regression. No adjustment will be made for multiple comparisons. Reporting of findings will be done in accordance with Consolidated Standards of Reporting Trials[39] and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis[36] guidelines.

Oversight and monitoring

Trial Management Committee (TMC)

The TMC consists of all chief investigators for each participating site, and the coordinating centre is located at the Mater Mothers' Hospital and Mater Research—University of Queensland. Participating sites include the Mater Mother's Hospital, Royal Brisbane and Women's Hospital, Sunshine Coast University Hospital and Gold Coast University Hospital. The TMC will oversee and plan the conduct of the study at each site including aspects of monitoring, recruitment, progress, data management, modifications to the study protocol, adverse event reporting, Human Research Ethics Committee (HREC) and local governance approvals, consideration of relevant information from new research, and implementation of recommendations from external bodies and reviewing committees, including the Independent Data and Safety Monitoring Committee (IDSMC). Such recommendations may include modification of the study protocol, or stopping of the trial based on interim analysis, or other relevant information or advice. The TMC will be responsible for communicating any changes to the protocol or study conduct to participating sites, investigators, registries, journals or regulators.

Independent Data and Safety Monitoring Committee (IDSMC)

A joint IDSMC who will oversee both RidStress 2 and iSEARCH (published in this *BMJ Open* issue and linked to this manuscript) has been established. The IDSMC will meet at least annually and comprises three perinatal care clinicians/researchers (one serving as Chair) and a biostatistician. All IDSMC members will be independent of sponsor, trial conduct and membership will be restricted to those that are free of significant conflicts of interest. The role of the IDSMC is to safeguard the interests of study participants by reviewing interim data on the primary outcome, adverse events and other outcome data after 50% recruitment or as appropriate (as per Peto *et al*, Haybittle, and Geller and Pocock).[37 40 41] There will be no adjustment to alpha for interim analyses. The IDSMC will provide the TMC a report outlining their recommendations.

Interim analyses of the primary composite outcome

The IDSMC will advise the TMC if they consider there is proof beyond reasonable doubt of net benefit or harm for the primary outcome, employing a commonly used formal threshold of p<0.001 for nominal significance, as recommended by Geller and Pocock.[41]

Interim analyses of mortality

The IDSMC will advise the TMC if they support the view that there is a difference in mortality due to intrapartum stillbirth and/or 28-day neonatal mortality identified as a deviation from the null indicated by a Haybittle-Peto boundary of 3 standard errors from the null, which is equivalent to p<0.0027,[37 40] which would be needed to justify recommending early stopping.

Safety and adverse event reporting

We will adhere to National Health and Medical Research Council guidelines for safety monitoring and serious adverse event (SAE) reporting in clinical trials involving therapeutic goods.[42–44] All SAEs occurring from the time of administration of the trial medication until hospital discharge will be reported to the sponsor with oversight provided by the IDSMC. Adverse events will be assessed for causality, as 'expected' or 'unexpected' with consideration given to the temporal relationship between administration of the trial medication and SAE. Possible adverse drug reactions (summarised in online supplemental appendix 2)[45] will be recorded.

In addition, the following maternal and neonatal events will also be reported as SAEs for this study:

Maternal SAEs:

1. Maternal intensive care unit admission.
2. Maternal hypotension (<60/40 mm Hg × three episodes) requiring medical intervention.
3. Major postpartum haemorrhage>1500 mL.
4. Persistent visual changes requiring ophthalmic review.
5. Maternal death prior to discharge from hospital.

Neonatal SAEs:

1. Admission to NICU for >48 hours.
2. Cord arterial pH<7.0.
3. Hypoxic ischaemic encephalopathy.
4. Neonatal seizure.
5. Intrapartum stillbirth.
6. Neonatal death prior to discharge from hospital.

Compliance and auditing

The trial will be conducted in compliance with full good clinical practice recommendations[46] and will be subject

to annual inspection and audit by Mater Misericordiae Limited under their remit as sponsor. The study will comply with all applicable laws and regulations and the principles laid down by the World Medical Association in the Declaration of Helsinki 2013. It is registered with the Australian and New Zealand Clinical Trial Registry. Trial results will be disseminated as soon as practical via presentations at clinical, academic and scientific meetings, peer-reviewed journals and general media. We will adhere to all relevant reporting guidelines.

Ethics and dissemination

Ethics approval was granted by the Mater Misericordiae Limited Human Research Ethics Committee (EC00332) on 11 September 2020. We plan to disseminate the results of this RCT through presentations at scientific meetings and peer-reviewed journals, adhering to all relevant reporting guidelines.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

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