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Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol

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ABSTRACT

Introduction Intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic–ischaemic brain injury and subsequent longer term disability. In many cases, hypoxia develops as a gradual process due to the inability of the fetus to tolerate the stress of parturition suggesting reduced fetoplacental reserve before labour commences. The fetal cerebroplacental ratio (CPR) is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. Similarly, circulating maternal levels of placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction. This paper outlines the protocol for the PROMISE Study, which aims to determine if the introduction of a prelabour screening test for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction of adverse perinatal outcomes.

Methods and analysis This is a single-site, non-blinded, individual patient randomised controlled trial of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Women with a singleton, non-anomalous pregnancy will be recruited after 34 weeks' gestation and randomised to either receive the screening test or not. Screened pregnancies determined to be at risk will be recommended induction of labour. Demographic, obstetric history and antenatal data will be collected at enrolment, and perinatal outcomes will be recorded after delivery. Relative risks and 95% CIs will be reported for the primary outcome. Regression techniques will be used to examine the influence of prognostic factors on the primary and secondary outcomes.

Ethics and dissemination This study has been reviewed and approved by the Mater Human Research Ethics Committee (Reference: HREC EC00332) and will follow the principles of Good Clinical Practice. The study results will be disseminated at national and international conferences and published in peer-reviewed journals.

Trial registration number ACTRN12616001009404; Pre-results.

Strengths and limitations of this study

- ► Will provide the first high-level evidence of the impact of a screening test combining the fetal cerebroplacental ratio and maternal placental growth factor on intrapartum fetal compromise and adverse neonatal outcomes.
- ► Single-site, randomised controlled trial in a high-income setting.
- ► Unable to blind participants or clinicians to randomisation due to nature of intervention.
- ► Sample size powered to detect a 40% reduction in a composite outcome indicative of significant perinatal asphyxia.

INTRODUCTION

Background

Globally, intrapartum complications are a major contributor to adverse perinatal outcomes, including stillbirth, hypoxic–ischaemic brain injury and subsequent longer term disability. Worldwide, of the 7.6 million deaths under 5 years of age, almost 9.4% are as a consequence of intrapartum-related complications mainly in low-income and middle-income countries, and it is estimated that globally almost 45% of stillbirths (approximately 1.3 million per annum) occur during the intrapartum period.[1] In Australia, hypoxic peripartum death is one of the top three causes of mortality in singletons >37 weeks.[2] Additionally, there is significant neonatal morbidity (neonatal encephalopathy, respiratory distress, acidosis and admission to the neonatal intensive care unit (NICU)) associated with intrapartum hypoxia. These compromised babies frequently require rapid delivery by emergency operative delivery that carries considerably more maternal risk than less urgent procedures. In Australia, emergency caesarean rates for intrapartum fetal compromise (fetal distress) range from 11% of all caesareans in Queensland to

16.3% in Tasmania.[2] Neonatal outcomes are also significantly poorer following emergency caesarean for fetal distress.[3]

In some term babies, intrapartum fetal compromise or hypoxia occurs as a result of unpredictable acute events such as uterine rupture, cord prolapse or placental abruption. However, most cases of asphyxia during labour occur due to a gradual decline in the ability of the fetus to tolerate the process of parturition. It is likely that these infants have decreased fetoplacental reserve prior to the onset uterine contractions. The underlying process causing this placental dysfunction is not completely understood but likely to be related to suboptimal fetal growth.[4 5] If delivery is not expedited, these infants are at serious risk of brain injury and subsequent permanent disability with hypoxic–ischaemic encephalopathy, a key risk factor for the development of cerebral palsy in term infants.[6] Labour is an asphyxial process, with contractions reducing blood flow in the uterine arteries and thus decreasing oxygen availability to the placenta and fetus.[7] This results in a gradual deterioration of the fetal condition reflecting a steady decline in the ability of the placenta to oxygenate the fetus as labour progresses. The fetus responds to uterine contractions with acute cerebral redistribution, evidenced by a reduced middle cerebral artery Pulsatility Index (MCA PI). This centralisation of blood flow is identical to that observed chronically in growth restricted fetuses. Some studies suggest that intrauterine pressures of just 35 mm Hg are enough to obliterate uterine artery end diastolic velocities,[8] resulting in reduced placental perfusion. Impaired placental transfer of oxygen and other substrates during labour is likely to be responsible for the 'fetal distress' that develops as a consequence of regular uterine contractions. However, up to 63% of babies who become distressed and suffer oxygen deprivation in labour have no apparent prior risk factors.[7]

The fetal cerebroplacental ratio (CPR) is the ratio of the MCA PI to the Umbilical Artery Pulsatility Index (UA PI). The CPR gradually rises until around the 34th week and subsequently slowly declines until term.[9] In some term small for gestational age (SGA) fetuses, the MCA PI is reduced despite normal UA Doppler indices (ie, a low CPR), and this is associated with poorer perinatal outcomes[10 11] and adverse neurobehaviour sequelae.[12] We[13–15] and others[16–18] have established that the CPR is an independent predictor of intrapartum fetal compromise, poor acid base status at birth and of neonatal unit admission at term. In addition, a low CPR may also reflect a failure of a fetus to reach its genetic growth potential at term,[19 20] despite having a normal birth weight. Furthermore, a low CPR has been shown to be associated with an increased risk of stillbirth regardless of the gestation or size of the baby.[21] An ongoing randomised controlled trial (RATIO37),[22] currently in the recruitment phase, aims to determine whether the addition of the CPR to standard ultrasound biometry measured at term can identify fetal growth restriction (FGR) due to placental insufficiency.

Circulating maternal levels of angiogenic factors such as placental growth factor (PlGF) are lower in pregnancies complicated by placental dysfunction.[23–25] PlGF belongs to the vascular endothelial growth factor family and is primarily produced by the placenta. It plays a key role in placental angiogenesis and vascular remodelling and is known to stimulate dilation of myometrial and uterine vessels.[26] This effect is particularly pronounced in uterine arteries during pregnancy, suggesting that PlGF contributes to vascular remodelling during gestation. During the first and second trimesters of pregnancy, low maternal levels of PlGF are linked to impaired placental development and angiogenesis, leading to multiple pregnancy complications including miscarriage, stillbirth, pre-eclampsia, SGA infants and FGR.[25 27] Low maternal PlGF levels are also predictive of pre-eclampsia and FGR when measured in late pregnancy.[24 28 29] PlGF may also help determine whether a fetus is constitutionally small or growth restricted with low PlGF levels associated with histopathological signs of placental underperfusion.[23 30] Furthermore, in women with SGA fetuses, a low PlGF measured in the third trimester is associated with adverse perinatal outcome (emergency caesarean for fetal distress and/or neonatal acidosis).[31] More recently, it has been reported that prelabour PlGF levels are significantly lower in women that developed intrapartum fetal compromise and have adverse neonatal outcome, even after excluding SGA fetuses.[32]

We have previously shown that a CPR threshold of <10th centile appears to be a good discriminator for identifying fetuses at risk of intrapartum compromise.[33] Our recent publication[34] assessing the utility of a screening test for intrapartum fetal compromise at term incorporating the CPR and maternal PlGF levels showed that the sensitivities, specificities and positive likelihood ratios for caesarean section for intrapartum fetal compromise were 100%, 86% and 7.14%, respectively. Combining both measures in the predictive model substantially improved the results of either element alone, raising the possibility that this might be a reasonable way to screen for this complication at term.

Justification for study and hypothesis

In most women, placental function is sufficient to allow appropriate fetal growth throughout pregnancy, however in some, it may not be adequate to meet the additional demands required in the last few weeks of pregnancy or during labour thereby predisposing these vulnerable fetuses to intrapartum compromise and subsequent risk of serious morbidity and mortality. A strategy to identify these infants is thus urgently needed. A screening test incorporating the CPR and maternal PlGF levels could identify these at-risk babies. Furthermore, if this screening strategy is combined with induction of labour for women that screen positive, it may reduce the risk of emergency operative birth and serious adverse neonatal outcomes.

OBJECTIVES

Primary objective

To determine if the introduction of a prelabour screening test at 37–38 weeks of gestation for intrapartum fetal compromise combining the CPR and maternal PlGF level results in a reduction in a composite measure of adverse perinatal outcomes (emergency caesarean for fetal compromise or severe acidosis at birth or 5 min Apgar score ≤5 or death).

Secondary objective

To determine if introduction of this screening test results in a reduction in overall operative delivery rates (instrumental and caesarean section) for fetal compromise and neonatal morbidity (defined as admission to the NICU for >48 hours or severe respiratory distress (respiratory support >4 hours)).

METHODS

Study design

This is a single-site (Mater Mothers' Hospital, Brisbane, Australia), non-blinded, individual patient RCT of a screening test performed at term, combining the fetal CPR and maternal serum PlGF. Our study protocol follows the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials guidance for clinical trials.[35]

Inclusion criteria

- Women aged between 18–45 years who are able to give informed consent.
- Singleton pregnancy between 34+0–37+6 weeks' gestation.
- Cephalic presentation.
- Planning a vaginal delivery.

Exclusion criteria

- Multiple pregnancy.
- Maternal body mass index (BMI) >40 kg/m^2.
- Previous caesarean section.
- Known fetal anomaly or aneuploidy.
- Known FGR (defined as estimated fetal weight (EFW) <10th centile and abnormal umbilical artery Dopplers).
- Known rupture of membranes.

Intervention

Once recruited, study participants will be randomised to either receive the screening test (intervention group) or not (control group). Figure 1 outlines the management for participants in both groups. Women in the control group will receive standard antenatal care (appropriate to her pregnancy) as per the hospital's policies and guidelines. The screening test will be a combination of two elements: an ultrasound scan measuring fetal CPR and blood test measuring maternal serum PlGF levels performed between 37+0 to 38+0 weeks' gestation.

Ultrasound parameters measured will include fetal biometry, UA PI and MCA PI. The pulsatility indices will be measured from an automated trace of at least three consecutive waveforms of the relevant vessel in the absence of fetal breathing movements or uterine contractions. The angle of insonation will be as close to zero degrees as possible. The UA PI will be recorded from a free-floating section of cord, and the MCA PI will be obtained from the proximal third of the vessel, taking care to avoid excessive transducer compression of the fetal head. Each parameter will be recorded three times, and a mean of these values will be used for data analysis. Maternal serum PlGF levels will be quantified using the DELFIA Xpress immunoassay (PerkinElmer, Turku, Finland). The DELFIA platform requires a 40 µL SST plasma sample and reports a concentration in the range of 7–4000 pg/mL with an overall coefficient of variation of 10.1%–5.1% (at 27.6 pg/mL and 74.2 pg/mL, respectively).

Based on published data from our group,[34] a screen positive result (identifying an at risk fetus) is defined as a CPR of ≤20th centile and maternal PlGF level ≤33rd centile. Any other combination is considered a screen negative result. Women who screen positive will be advised of the increased risk of intrapartum fetal compromise, and induction of labour within 7 days of the test

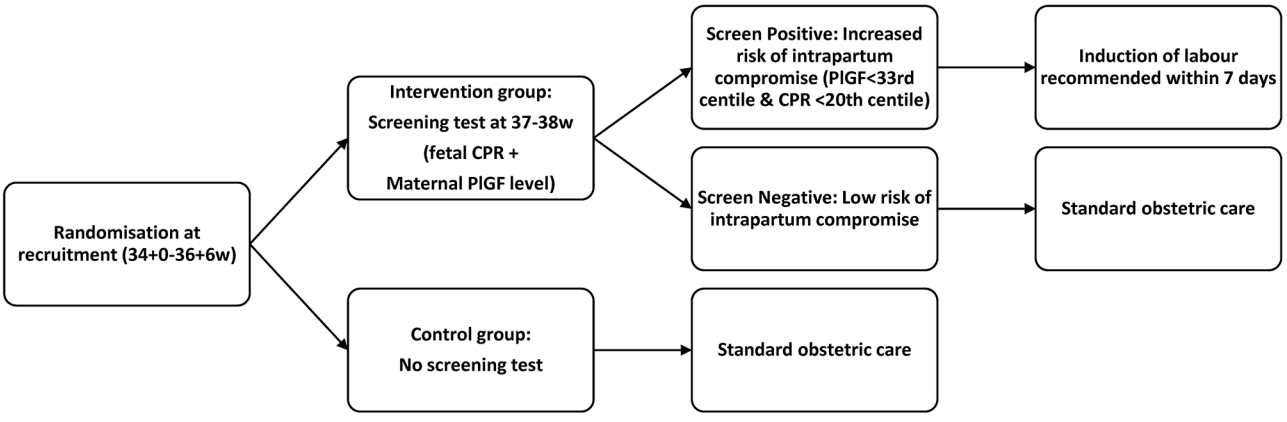

Figure 1 Flow chart of study intervention and participant management. CPR, cerebroplacental ratio; PlGF, placental growth factor.

result will be recommended. If she chooses not to be delivered, then weekly fetal surveillance at the discretion of the treating obstetric team will be offered until birth occurs. Women who screen negative will receive standard obstetric care, appropriate to her pregnancy. Intrapartum care (including induction of labour if applicable) for all participants will be as per the hospital's policies and guidelines; however, all women who screen positive will receive continuous electronic fetal heart rate monitoring in labour. The only result that will be released to obstetric caregivers is the designation—'screen positive' or 'screen negative'. However, if the ultrasound scan detects a malpresentation, EFW <5th or >95th centile or pathological umbilical artery Dopplers (absent or reversed end diastolic flow), the obstetric team caring for the woman will be informed of these findings.

Data collection

Demographic and antenatal data will be collected for all participants from the maternity database and stored in an anonymised and secure format. Collected data will include maternal age, ethnicity, socioeconomic status, BMI, history of smoking, previous pregnancy outcomes including mode of delivery and any complications. For the current pregnancy, data collected will include mode of conception, blood pressure at booking, first trimester screening results, presence of hypertensive disorders of pregnancy, diabetes mellitus, thyroid dysfunction, antepartum haemorrhage and maternal medications.

Primary outcome

The primary outcome is a composite measure of adverse outcomes: emergency caesarean section for intrapartum fetal compromise or neonatal acidosis (defined as cord arterial pH <7.1 or lactate >6 mmol/L or base excess ≤−12 mmol/L) or Apgar score ≤5 at 5 min or stillbirth or neonatal death within 28 days. These specific outcomes have been chosen as they indicate significant perinatal asphyxia.

Secondary outcomes

Secondary outcomes include overall operative delivery rates (instrumental and caesarean section) for fetal compromise and maternal and neonatal morbidity (defined as admission to the NICU for >48 hours or severe respiratory distress (respiratory support >4 hours)).

Sample size calculation

The proposed sample size is based on previous pilot data from our group that found 17.6% of women experienced the primary composite outcome measure. Anticipating a 40% reduction in the proportion of adverse events to 10.6% in the screening test intervention group, a sample size of 382 women is required in each group (type 1 error of 5% and power of 80%). Assuming a 10% drop out rate, we plan to recruit a total of 840 women. There are >5500 publicly funded births at the Mater Mother's Hospital each year. With an estimated 70% of women being eligible to participate, it is expected that the required sample size can be recruited within 2 years.

Study review and data monitoring

The study will be conducted in accordance with the principles of Good Clinical Practice. A Data Safety and Monitoring Committee (DSMC) will be established to oversee any adverse events arising from this study. Members of the DSMC will be external to and independent of the research group and will include an obstetrician, neonatologist and statistician. The study results will be disseminated at national and international conferences and published in peer-reviewed journals. This study has been registered as a clinical trial with the Australian New Zealand Clinical Trials Registry (ANZCTR Trial ID: ACTRN12616001009404 and WHO UTN: U1111-1181-3852). Recruitment for the study commenced in April 2017, and the study is planned to continue until May 2019.

Randomisation

Randomisation will be performed using the STATA V.13 programme and will be undertaken by an epidemiologist within the Mater Research Institute. Participants will be randomised to either screening test or no screening test in equal numbers (1:1) in block sizes of four and six to yield the appropriate sample size. Allocations will be concealed in opaque envelopes until individual randomisation occurs.

Statistical analysis

Outcome comparisons for women and infants will be analysed for the primary and secondary outcomes on an 'intention to treat' basis, according to treatment allocation at randomisation. The relative risks and 95% CIs will be reported for the primary outcome (composite adverse outcome), and the number needed to treat to prevent one adverse outcome will be calculated. Subgroup analysis comparing either proportions or means, as appropriate, will be undertaken for elements of the primary composite outcome and secondary outcomes. Regression techniques will be used to examine the influence of prognostic factors on the major primary outcome and secondary outcomes.

Patient and public involvement

One hundred women from a tertiary antenatal outpatient setting were invited to complete an anonymised patient acceptability questionnaire to elicit their views in regards to participating in an RCT of a screening test for intrapartum fetal compromise. The results of this survey were used to inform the study design. All study participants will be invited to nominate if they would like to receive an email outlining the results of the study after completion.

Contributors HS is the study coordinator, contributed to study planning, will collect and analyse the data and will participate in reporting the data. VC contributed to study planning and will participate in report of the data. SK is the principal investigator (PI) for the study.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study protocol, patient information and consent form and other accompanying material that will be provided to participants have been reviewed and approved by the Mater Human Research Ethics Committee (Reference No: HREC EC00332).

Provenance and peer review Not commissioned; externally peer reviewed.

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