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Revealed versus concealed criteria for placental insufficiency in an unselected obstetric population in late pregnancy (RATIO37): randomised controlled trial study protocol

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ABSTRACT

Introduction Fetal growth restriction (FGR) affects 5%–10% of all pregnancies, contributing to 30%–50% of stillbirths. Unfortunately, growth restriction often is not detected antenatally. The last weeks of pregnancy are critical for preventing stillbirth among babies with FGR because there is a pronounced increase in stillbirths among growth-restricted fetuses after 37 weeks of pregnancy. Here we present a protocol (V.1, 23 May 2016) for the RATIO37 trial, which evaluates an integrated strategy for accurately selecting at-risk fetuses for delivery at term. The protocol is based on the combination of fetal biometry and cerebroplacental ratio (CPR). The primary objective is to reduce stillbirth rates. The secondary aims are to detect low birth weights and adverse perinatal outcomes.

Methods and analysis The study is designed as multicentre (Spain, Chile, Mexico,Czech Republic and Israel), open-label, randomised trial with parallel groups. Singleton pregnancies will be invited to participate after routine second-trimester ultrasound scan (19^{+0}–22^{+6} weeks of gestation), and participants will be randomly allocated to receive revealed or concealed CPR evaluation. Then, a routine ultrasound and Doppler scan will be performed at 36^{+0}–37^{+6} weeks. Sociodemographic and clinical data will be collected at enrolment. Ultrasound and Doppler variables will be recorded at 36^{+0}–37^{+6} weeks of pregnancy. Perinatal outcomes will be recorded after delivery. Univariate (with estimated effect size and its 95% CI) and multivariate (mixed-effects logistic regression) comparisons between groups will be performed.

Ethics and dissemination The study will be conducted in accordance with the principles of Good Clinical Practice. This study was accepted by the Clinical Research Ethics Committee of Hospital Clinic Barcelona on 23May 2016. Subsequent approval by individual ethical committees and competent authorities was granted. The study results will be published in peer-reviewed journals and disseminated at international conferences.

Trial registration number NCT02907242; pre-results.

Strengths and limitations of this study

- This is the first randomised study examining the impact on perinatal heath of evaluating the fetal cerebroplacental ratio to select patients for labour induction.
- The sample size is powered to detect clinically relevant reductions in hard adverse perinatal events, including perinatal death.
- The generalisability of this study is supported by the multicentre design, covering medium-income to high-income settings.
- The nature of the intervention makes it impossible to blind participants,
- Follow-up of the offspring is limited to the neonatal period.

INTRODUCTION

Background and rationale

Fetal growth restriction (FGR) is defined as a failure to reach the growth potential. FGR affects 5%–10% of all pregnancies and contributes to 30%–50% of stillbirths.[1] In most cases, FGR is due to placental insufficiency.[2] Population-based studies have endorsed not only the linkage between FGR and increased risk of mortality and morbidity in the perinatal period, but the risk of delayed consequences into childhood and adulthood.[3–5] Therefore, antenatal identification of FGR is crucial to optimise the timing of delivery and to reduce perinatal risks.[5 6] Unfortunately, growth restriction often is not detected antenatal. During routine clinical practice, as many as 75% of babies at risk for FGR are not recognised before delivery.[7] Notably, the gestational age at birth of FGR-related but undetected stillbirths is 280 days,

while it is 270 days in detected cases.[5] This indicates that the last weeks of pregnancy are critical to prevent stillbirth for FGR babies. This conclusion is further supported by large-scale studies showing that there is a pronounced increase in stillbirths among small fetuses after 37 weeks of pregnancy.[8]

Antenatal screening for small for gestational age/FGR

The first step to detect FGR due to placental insufficiency is to detect fetuses at risk for small for gestational age (SGA). SGA at birth is defined as birth weight below the 10th percentile for local standards at each study site. The typical third trimester strategy to monitor growth involves fetal weight measurement. However, most SGA infants are not detected in low-risk populations using this strategy.[9] Although the use of strictly defined methodology and maternal-customised standards could potentially improve fetal weight measurement,[10] evidence supporting its use is lacking. Routine third trimester ultrasound scan performs better than selective scans based on risk factors (evidence level IB).[11] In addition, one random controlled trial reported that a 36-week scan provided better prediction of SGA at birth than a 32-week scan.[12] The risk of delaying the scan after 36 weeks is that the stillbirth rate increases among SGA babies after 37 weeks.[8]

Once SGA is suspected, healthcare providers should determine whether the fetus has constitutional smallness or true FGR using one of several possible strategies. The rationale of customisation adjusts for fetal growth standards with respect to maternal characteristics that influence fetal size, such as parity, maternal weight and height and ethnicity. By determining an individualised growth potential for each fetus, constitutional smallness could be differentiated from FGR. Although this concept has been shown to be useful in neonates to predict adverse neonatal outcomes,[13] customised standards have not been shown to improve the detection of placental insufficiency in fetuses.[14]

Fetuses destined to have an adverse outcome have a slower growth rate than those with normal outcomes.[15] In SGA babies, some studies have found that growth rate performs better as a marker than other fetal and maternal parameters.[11 16] However, there is controversy regarding the best methodology to use for longitudinal growth measurement, and multiple strategies have been used including conditional assessment, individualised longitudinal growth, growth rates and growth trajectories. Another limitation of longitudinal growth is that assessments with intervals <3 weeks are prone to result in a large proportion of false positives.[17] This problem is critical when SGA is diagnosed near term because there is not enough time remaining to properly assess longitudinal growth.

In early-intrauterine growth restriction, Doppler assessment of the umbilical artery (UA) can reduce perinatal mortality and morbidity,[18] and is a standard of care in fetal monitoring. By contrast, in late SGA, the UA does not accurately reflect placental insufficiency.[19] Under hypoxic conditions, the fetus redistributes its flow towards the brain, a phenomenon called brain sparing. This is reflected in the middle cerebral artery (MCA) flow, which shows decreased pulsatility during Doppler evaluation. A proportion of late SGA babies develop abnormal MCA and, in a more pronounced way, abnormal cerebroplacental ratio (CPR),[20] which is the ratio between MCA and UA pulsatility index (PI). The evidence suggests that SGA babies with abnormal CPR have a 10-fold increased risk of adverse outcome,[21] which indicates that CPR is a useful marker to differentiate constitutional smallness from late FGR.

Management and delivery of late-SGA babies

A random controlled trial shows that systematic induction of late-SGA babies at 37–38 weeks does not improve perinatal and neurodevelopmental outcomes.[22 23] However, induction at this gestational age does not worsen neonatal outcomes and may be more cost-effective than later induction; therefore, most guidelines recommend delivery of SGA babies at risk of placental insufficiency (growth-restricted babies) after 37–38 weeks, which prevents those rare but devastating cases of stillbirth that occur during the last weeks of pregnancy. There is consensus that abnormal CPR is a defining criterion for FGR in SGA babies.[24]

Only some FGR babies are small

It is biologically implausible that all cases of placental insufficiency occurred in babies with birth weights below the 10th percentile. In fact, perinatal mortality remains higher in babies between the 10th and the 50th percentile of birth weight,[25] suggesting that a proportion of cases of placental insufficiency exhibit growth within normal ranges. There is evidence showing that normally growing babies with abnormal CPR have a higher frequency of placental insufficiency as determined by abnormal uterine artery Doppler,[26] which may impair their neurobehaviour at birth.[27] Recent work shows that CPR is associated with perinatal mortality, independently of birth weight.[28] Finally, there is evidence that abnormal CPR before birth is associated with the occurrence of fetal distress during labour,[29] supporting the concept that CPR reflects latent placental insufficiency.

Justification for the study

Although fetal size and CPR independently correlate with adverse perinatal outcome, it has not been determined whether a strategy of labour induction based on these parameters has the potential to prevent stillbirths. It is necessary to obtain evidence in support of this hypothesis before recommending the widespread use of this strategy.

HYPOTHESIS

A proportion of fetuses with normal growth (as defined per current standards) has placental insufficiency and restricted growth potential. These fetuses exhibit biophysical changes that can be detected by abnormal CPR. The

combination of abnormal CPR with fetal biometry to detect fetuses affected by FGR could identify the group of at-risk babies. Labour induction at term may prevent adverse outcomes for these babies.

OBJECTIVES

Primary objective

The primary objective is to determine whether the addition of CPR Doppler evaluation to the standard ultrasound biometrical measurements can reduce perinatal mortality by efficiently selecting women for labour induction.

Secondary objectives

i. to determine whether the addition of CPR Doppler evaluation to the standard ultrasound biometrical measurements decreases mild and severe adverse perinatal outcomes after labour induction;
ii. to determine whether the addition of CPR Doppler evaluation to the standard ultrasound biometrical measurements decreases neurological morbidity after labour induction;
iii. to determine whether the addition of CPR Doppler evaluation to the standard ultrasound biometrical measurements decreases non-neurological morbidity (defined as prolonged neonatal intensive care unit (NICU) stay without criteria of neurological morbidity) after labour induction;
iv. to evaluate the predictive capacity of an integrated strategy based on the combination of fetal biometries and CPR at 36–37 weeks to detect prenatal low birth weight.

METHODS

Study setting

The study will be conducted within academic hospitals with specialist experience in managing FGR, in Spain (Hospital Clinic Barcelona), Chile (Hospital Clinico Universitario de Santiago Chile), Mexico (Hospital of Querétaro) Czech Republic (Palacky University Hospital in Olomouc, Charles University Hospital in Prague) and Israel (Lis Hospital for Women, Tel Aviv). Each of these hospitals attends >3000 deliveries and performs >10 000 fetal ultrasounds per year.

Trial design

This is a multicentre, open-label, randomised trial with parallel groups. The study design adheres to the SPIRIT quality standard criteria for randomised trials.[30]

Eligibility criteria

The following five criteria were used for inclusion in the study: (i) viable singleton non-malformed fetus at the routine second trimester ultrasound, (ii) available first trimester scan (with embryo crown-rump length measurement), (iii) absence of adverse medical or obstetric history, (iv) maternal age at recruitment>18 years and (v) capacity to give informed consent. The following three criteria were used for exclusion from the study: (i) abnormal karyotype, (ii) structural abnormalities and (iii) congenital infections.

Exclusion criteria

Women with obstetrical complication arising before 37 weeks (as premature rupture of membranes (PROM)) prompting delivery will be excluded.

Intervention

Trial participants will be allocated to revealed or concealed third trimester (36–37 weeks) CPR evaluation. In the concealed group, management will adhere to the current standard for managing SGA pregnancies. In the revealed group, CPR data obtained from Doppler evaluation will be integrated into the criteria used for decisions regarding labour induction. The flow chart in figure 1 illustrates the management strategy following intervention.

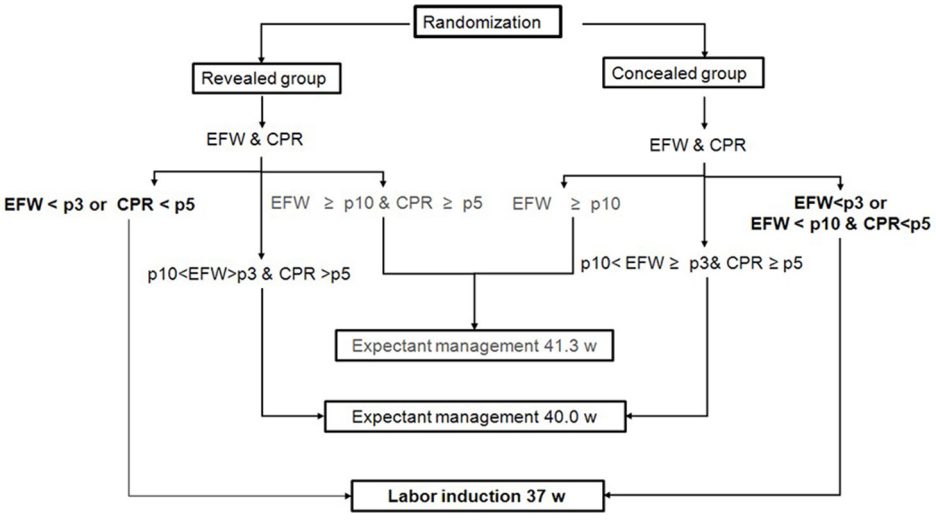

Figure 1 Flow chart of study intervention and management. CPR, cerebroplacental ratio; EFW, estimated fetal weight.

Predictive variables

The predictive variables include fetal biometries, amniotic fluid, Doppler evaluation, UAPI and MCA PI. The fetal biometries include biparietal diameter, head circumference, abdominal circumference and femur length. These will be measured according to standardised procedures.[31] The Hadlock formula will be used to calculate estimated fetal weight, which will qualify for fetal SGA if it is below the 10th percentile.[32] Amniotic fluid will be measured in the deepest vertical pocket (an abnormal value is defined as<20 mm). Doppler measures will be obtained in the absence of fetal movements and with voluntarily suspended maternal breathing. Doppler parameters will be measured automatically from three or more consecutively similar waveforms, with the angle of insonation as close to 0° as possible. UA PI will be measured from a free-floating cord loop. MCA PI will be measured in a transversal view of the fetal head, at the level of its origin from the circle of Willis. The latter two parameters will be used to derive the CPR as follows: MCA PI/UA PI. CPR will be considered as abnormal when it is below the fifth percentile.[33]

OUTCOMES

Primary outcome

The primary outcome will be perinatal mortality from inclusion to +28 neonatal days.

Secondary outcomes

Four secondary outcomes will be recorded, including mild adverse perinatal outcome, severe neurological morbidity, severe non-neurological morbidity and SGA at birth. Mild adverse perinatal outcome is defined as any of the following: (i) caesarean section for fetal distress (defined according local protocols), (ii) 5 min Apgar score<7, (iii) neonatal acidosis at birth (UA pH<7.15 and base excess> −12 mEq/L) or (iv) admission to the neonatal unit. Severe neurological morbidity is defined as any of the following: (i) seizure,[34] (ii) interventricular haemorrhage >grade II,[35] (iii) periventricular leukomalacia[36] or (iv) hypoxia-ischaemia or encephalopathy.[34] Severe non-neurological morbidity is defined as any of the following: (i) prolonged NICU stay (>10 days) without criteria of neurological morbidity, (ii) necrotising enterocolitis,[34] (iii) acute renal failure (serum creatinine>1.5 mg/dL) or (iv) cardiac failure (requiring ionotropic agents). SGA at birth is defined as birth weight below the 10th percentile for local standards at each study site.

Participant timeline

Table 1 shows the study timeline.

Sample size

The required sample size was estimated as follows. For a 3‰ reduction of the stillbirth rate (from 5‰ to 2‰), assuming a type I error of 5% and aiming for a power of 80%, a total of 11 582 participants (5791 per arm) are required. The participating centres attend a total of 12 000 deliveries per year. Assuming that 50% of women are eligible and willing to participate, it is expected that the required sample size can be achieved within 2 years.

Allocation

An online service (http://www.randomization.com) was used to generate randomised sequences in blocks of 100 participants. This ensured a balanced distribution within the two study arms, stratified for participating site. The

Table 1 Study timeline

	Study period			
	Enrolment 19–23 weeks	Allocation 20–24 weeks	Postallocation 36–37 weeks	Close-out 28 days after delivery
Timepoint	T1		T2	T3
Eligibility screen	X			
Informed consent	X			
Allocation 20–24 weeks		X		
Interventions				
Concealed			X	
Revealed			X	
Assessments				
Sociodemographic data		X		
Medical history		X		
Prenatal evaluation (ultrasound biometries)		X	X	
Doppler assessment			X	
Amniotic fluid assessment			X	
Perinatal outcome				X

allocation sequence will be sequestered internally by a Clinical Trials Unit.

At the time of routine second trimester scans and after enrolment, recruiting physicians will obtain the allocation group from a web-based system. Women who decline consent for randomisation but authorise the use of their medical data will be included in the database. These data will be used for external validity testing of the trial. Due to the nature of the intervention, it is not possible to blind participants, obstetricians or outcome assessors with respect to the study group.

Data collection

The coordinator at each site will collect sociodemographic data and first and second trimester ultrasound data. Participants will be scheduled for a third trimester ultrasound at 36+0 to 37+6 weeks; these data will be used to obtain fetal biometric data, measure the amniotic fluid volume in the deepest vertical pocket and calculate CPR. Perinatal outcomes will be recorded after delivery and at +28 days.

Participant data for this study will be anonymised and entered into an electronic case report form (e-CRF) hosted in a secured website by each site coordinator. Logic and range rules operate in the e-CRF to minimise errors in entering the information.

Data monitoring

An independent Clinical Trial Unit will perform offline data auditing every 6 months to check for missing information and errors. Umbilical and middle cerebral Doppler images will be requested from a random sample of 25 women every 6 months to check for accuracy according the following criteria: (i) location site (UA free-loop and proximal portion of the MCA); (ii) size of the Doppler spectral gate (equivalent to the vessel diameter); (iii) scale velocity of the pulsed Doppler, which should result in a waveform height equivalent to at least 2/3 of the *y*-axis; and (iv) automatic calculation of the PI from at least three consecutively similar waveforms. The sites will be notified of any deviation from the standard recommendations for amendment.

Statistical analysis

Statistical analysis will be based on the originally assigned groups (intention-to-treat). A binomial distribution model will be used to determine the 95% CI of proportions. Student's t-test (or non-parametric Mann-Whitney U test) and Pearson's χ^2 test or linear-by-linear χ^2 test (for trends across ordered categories) will be performed for univariate between-group comparisons of quantitative or qualitative variables, respectively. A mixed-effects logistic regression analysis of the incidence of stillbirth with fixed effects for allocation group and random effects for the study centre will be used. Logistic regression also will be used to determine which of the variables have a significant contribution for predicting stillbirth, low birth weight and adverse perinatal outcome. In these regression models, stepwise algorithms will be performed to select variables at p-value cut-off of 0.05 for inclusion and 0.1 for exclusion, with tolerance level>0.01. Goodness-of-fit models will be assessed by calculating Nagelkerke's R^2 and by performing a Hosmer and Lemeshow's test. Performance of the models also will be evaluated by constructing receiver operating characteristic (ROC) curves. A subanalysis will be carried out in patients undergoing an elective caesarean section. ROC curves will be compared pairwise using the DeLong procedure. Open-source software (The R Foundation for Statistical Computing) will be used for all computations and graph construction (R V2.15.1).

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Contributors MR is the project monitor, contributed to the study planning and will participate in the report of the data. RC, MP, ML and LK are coordinators at their respective sites, contributed to the study planning and will participate in the report of the data. MC and MM contributed to the conducting and will report the data. FF is the general coordinator and PI of the project. EG is co-principal investigator of the study.

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Competing interests None declared.

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