BMJ Open

Cook's balloon versus dinoprostone for Labour induction of term pregnancies with fetal GROWth restriction: study protocol for a randomised controlled trial in tertiary maternity hospitals in Spain (COLIGROW study)

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To cite: Herraiz I, Meler E, Mazarico E, *et al*. Cook's balloon versus dinoprostone for Labour induction of term pregnancies with fetal GROWth restriction: study protocol for a randomised controlled trial in tertiary maternity hospitals in Spain (COLIGROW study). *BMJ Open* 2024;**14**:e089628. doi:10.1136/bmjopen-2024-089628

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-089628).

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Received 04 June 2024
Accepted 09 September 2024

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ABSTRACT

Introduction Fetal growth restriction (FGR) affects about 3%–5% of term pregnancies. If prenatally detected and anterograde umbilical artery flow is preserved (stage I), it is recommended to deliver at term (≥ 37+0 weeks). In the absence of contraindications, the vaginal route is preferred, and labour induction is usually required. It has been postulated that mechanical methods for cervical ripening may have an optimal profile for the induction of term FGR fetuses since they are associated with less uterine stimulation than the standard pharmacological methods, and therefore, could be better tolerated by fetuses with reduced placental reserve. This study aims to evaluate whether cervical ripening with a Cook's balloon for the induction of labour from 37+0 weeks of gestation in the stage I FGR manages to increase the rate of vaginal delivery compared with vaginal dinoprostone.

Methods and analysis This will be an open-labelled, randomised, parallel-group clinical trial to be held in five Spanish maternities. Women aged ≥18 years with singleton pregnancies complicated with stage I FGR (defined as the presence of at least one of these two criteria: (1) estimated fetal weight (EFW) <3rd percentile; (2) EFW <10th percentile and at least one of the following: (2.1.) umbilical artery pulsatility index >95th percentile and presence of antegrade end-diastolic flow or (2.2.) Cerebroplacental ratio <5th percentile), gestational age dated by first-trimester ultrasound ≥37+0 weeks at the time of labour induction, cephalic presentation, unfavourable cervix (Bishop score <7), intact fetal membranes, no previous caesarean section and no maternal or fetal contraindications for vaginal delivery or labour induction will be 1:1 randomised by centre to labour induction with Cook's balloon (experimental arm) or dinoprostone (control arm). FGR cases with evidence of non-placental origin (major structural fetal malformations, chromosomal anomalies or congenital infection) will be excluded. The primary outcome is the achievement of a vaginal delivery and it will be assessed by comparing the rates of vaginal delivery in each group using the one-sided χ^2 test at an alpha level of 0.025. The sample size has been estimated to observe an expected 84% of vaginal deliveries with Cook's balloon vs 62% with dinoprostone. Therefore, a total of 172 patients (86 per arm) are required (power of 90%, alpha level of 0.025, assuming a percentage of losses of 5%). The efficacy analysis will be performed in the intention-to-treat population. An interim analysis using a two-stage sequential design with the O'Brien-Fleming method will be applied.

Ethics and dissemination The trial was registered in the European Union drug regulating authorities' clinical trials database (EUDRACT) (2021-001726-22) and received approval from the local Research Ethics Committee (21/728) and the Spanish Agency of Medicines and Medical Devices (AEMPS). AEMPS classified the study as a low-intervention trial. The study will be conducted

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multicentre randomised clinical trial to compare Cook's balloon versus dinoprostone for achieving a vaginal delivery in term pregnancies with fetal growth restriction (FGR).
⇒ All selected cases will meet the currently accepted Delphi criteria for diagnosing FGR in singleton pregnancies, thus avoiding the inclusion of constitutionally small for gestational age fetuses.
⇒ An intention-to-treat analysis will be performed so that the results reflect the reality of clinical practice.
⇒ Maternal satisfaction with the process of induction, delivery and immediate post partum will be assessed through the Mackey childbirth satisfaction rating scale.
⇒ We have assumed an absolute reduction in the risk of caesarean section of 22%, based on our retrospective data, which could be overoptimistic and expose us to a type II error.

in compliance with the principles of Good Clinical Practice. The study results will be disseminated through workshops and national/international conferences and published in peer-reviewed journals. In addition, they will be disclosed to patients and the public in understandable language through study newsletters and press releases to news and social media.

Protocol version V.1.1, 18 May 2023.

Trial registration numbers EUDRACT 2021-001726-22 and NCT05774236.

INTRODUCTION

Fetal growth restriction (FGR) is a situation in which the fetus fails to reach its intrinsic growth potential, usually due to placental insufficiency.[1] Mild forms of FGR that preserve anterograde flow in the umbilical arteries (UA), that is, stage I FGR, are the most prevalent (70%–80%). The greatest risk for these fetuses appears once they reach term when other stressful situations are added to their situation of relative hypoxia, such as the appearance of contractions and funicular compression. Thus, it has been shown that from 37 to 38 weeks the risk of stillbirth increases[2] and it is advised not to exceed this threshold to indicate the induction of labour.[3 4]

Detection of FGR is not easy in clinical practice. A key aspect is to differentiate it from the constitutionally small for gestational age fetus, whose prognosis is similar to that of the general population. In this sense, the role of Doppler patterns of haemodynamic deterioration has been extensively investigated.[5] Thus, it has been observed that in stage I FGR that reach term pregnancy the degree of malnutrition is lower, and the haemodynamic alterations are usually more subtle than in cases that progress to absent or reverse flow, as a consequence of a milder placental insufficiency.[4] However, as the pregnancy reaches its term, fetal respiratory demands increase exponentially and tolerance to hypoxia is lower, which in the haemodynamic study of the fetus is expressed as a redistribution of flows towards the brain territory to prioritise its oxygenation. The Doppler parameter that best reflects this phenomenon of brain-sparing is the cerebroplacental ratio (CPR), which results from dividing the resistance in the middle cerebral artery by the resistance in the UA. To date, a broad consensus has already been achieved among experts to use CPR <5th percentile as a diagnostic criterion for FGR after 32 weeks of gestation.[6] Furthermore, in our experience[5] and that of others,[7] the presence of a CPR <5th percentile in term FGR fetuses is associated with fetal distress during labour and worse perinatal outcomes.

Attempting a vaginal birth through labour induction is by consensus the most reasonable option among pregnancies complicated with stage I FGR,[8] taking into account the multiple advantages of the vaginal route over an elective caesarean section. In the case of FGR, some of these benefits are especially relevant for the health of the newborn whose growth has been restricted in intrauterine life, such as the facilitation of skin-to-skin contact and the early initiation of breast feeding.[9]

Induction of labour in stage I FGR presents good results in terms of achieving a vaginal delivery, although these fetuses have an increased risk of caesarean section due to fetal distress. Since mechanical methods for cervical ripening in the first phase of labour induction (Foley catheter and Cook's balloon) are associated with less uterine stimulation with a lower rate of tachysystole than prostaglandins, they have been proposed as suitable for cervical ripening in FGR since they could reduce the risk of fetal distress.[10 11] Our observations support this hypothesis in a 'before and after' retrospective study on 148 cases of singleton pregnancies with stage I FGR undergoing induction of labour with cervical ripening, the rate of caesarean sections due to suspected fetal distress decreased after switching from vaginal dinoprostone to mechanical methods (26.0% vs 7.0%, p<0.01).[12] However, these promising results must be endorsed by a randomised clinical study to evaluate the impact on clinical practice. To our knowledge, this will be the first clinical research study that compares cervical ripening using mechanical methods (Cook's balloon) with cervical ripening using pharmacological methods (vaginal dinoprostone) for the induction of full-term singleton pregnancies complicated with FGR. This will cover the current lack of knowledge about what is the most suitable method to perform cervical ripening in this population.

HYPOTHESIS

In the induction of labour for stage I FGR, cervical ripening with Cook's balloon obtains a higher rate of vaginal deliveries than ripening with vaginal dinoprostone, safely for the mother and the newborn.

Null hypothesis (H0): rate of vaginal birth with Cook's balloon ≤rate of vaginal birth with vaginal dinoprostone.

Alternative hypothesis (H1): rate of vaginal birth with Cook's balloon >rate of vaginal birth with vaginal dinoprostone.

OBJECTIVES

Primary objective

To evaluate, through a clinical trial study, whether cervical ripening with a Cook's balloon for the induction of labour from 37+0 weeks of gestation in the stage I FGR manages to increase the rate of vaginal delivery compared with the use of vaginal dinoprostone.

Secondary objectives

1. Effectiveness:
   - To compare the rate of caesarean sections due to suspected fetal distress.
   - To analyse the mean time interval between the onset of cervical ripening and delivery.
2. Safety:
   - To evaluate the neonatal morbidity through the MAIN (morbidity assessment index for newborns)

score,[13] the presence of neonatal acidosis and neonatal intensive care unit (NICU) admission.

3. Satisfaction:
   - To assess the maternal satisfaction through the Mackey childbirth satisfaction rating scale.

METHODS AND ANALYSIS

Study design

This is a multicentre randomised, controlled, open-label, superiority trial with two parallel groups. Patients are randomised in a 1:1 ratio. The intervention is carried out with a medical device with CE marking and used for its intended purpose. Blinding of participants and caregivers is not possible since the appearance, insertion method and management of the two compared methods of cervical ripening are different in nature. The study is independent as it is conducted by the principal investigator together with the Spanish Clinical Research Network (SCReN) platform and only supported by a public health grant. The trial follows the principles of the Declaration of Helsinki and Good Clinical Practice. The protocol adheres to the recommendations of the Standard Protocol Items: Recommendations for Interventional Trials initiative (online supplemental material).[14]

Study period and setting

The competitive recruitment started in March 2023 from three centres in Spain (Hospital 12 Octubre, Hospital Clinic I Provincial, Hospital Sant Joan de Déu, the last two being legally integrated into the Center of Maternal Fetal and Neonatal Medicine of Barcelona (BCNatal)). From January 2024, two additional centres (Hospital Vall d'Hebron and Hospital Virgen de la Arrixaca) have been incorporated to reach target sample size. All of them are tertiary hospitals with large referral maternity wards that provide care to more than 3500 births per year.

Participants

Pregnant women with a singleton pregnancy and a fetus prenatally diagnosed with stage I FGR,[4] with an obstetric indication for planned term delivery by induction of labour and an unfavourable cervix will be candidates to participate. They must meet all the inclusion criteria and none of the exclusion criteria:

1. Inclusion criteria:
   - Singleton pregnancy.
   - Age ≥18 years.
   - Gestational age dated by first-trimester ultrasound ≥37+0 weeks at the onset of labour induction.
   - Cephalic presentation.
   - Stage I FGR is defined as the presence of at least one of these two criteria:
     1. EFW<3rd percentile.
     2. EFW <10th percentile and at least one of the following:
        (2.1) Umbilical artery pulsatility index >95th percentile (and presence of antegrade end-diastolic flow).
        (2.2) CPR<5th percentile.
   - Bishop score <7.
   - Intact fetal membranes.
   - No previous caesarean section.
   - No maternal or fetal contraindications for vaginal delivery or labour induction.
2. Exclusion criteria:
   - Major fetal malformation.
   - Fetal genetic abnormality.
   - Fetal congenital infection.

The EFW is calculated using Hadlock's formula,[15] and the corresponding percentile adjusted for gestational age and gender is derived from a standard chart for a Spanish population.[16] Gestational-age-based reference ranges for the umbilical artery pulsatility index[17] and CPR[18] percentile values are used. All calculations are available at https://fetalmedicinebarcelona.org/calc/.

Study investigators will screen for eligibility to all patients at each centre who are identified as meeting the inclusion and exclusion criteria during FGR follow-up visits from 36+0 weeks onwards. A list of all candidates will be compiled in the investigator's respective files. They will be verbally informed about the study by an investigator of the study using simple language. The patient information sheet and informed consent form (online supplemental material) will be given to them to read and decide if they voluntarily wish to participate, leaving appropriate time to ask questions and make an informed decision. Once the informed consent has been signed and dated by both the participant (or legally acceptable representative if necessary) and the investigator in real time, a copy will be given to the patient, and the participant will be considered to be included in the study. The other copy is filed with the study documents. Then, the pregnant woman will be scheduled for induction of labour on a day between 37+0 and 37+6 weeks of gestation or, if the diagnosis of FGR is made at 37+5 weeks or later, induction will begin within 48 hours of diagnosis.

Intervention

After hospital admission, an examination of the cervix will be performed to confirm the need for cervical ripening (Bishop score <7) and to rule out spontaneous premature rupture of membranes. Cephalic fetal presentation and absence of placenta previa will be also confirmed by ultrasound scan. If the patient no longer meets the inclusion criteria, she will not be suitable for randomised and will be considered a selection failure. If she still meets the conditions for cervical ripening, she will be 1:1 randomised and allocated to one of the following arms:

1. Experimental arm (mechanical method): Cook Cervical Ripening Balloon with Stylet (184000, Spencer, Indiana, USA) is intended to be used for mechanical dilation of the unfavourable cervix. It possesses the certification of the CE marking as a class IIa medical device and in this study is applied according to its intended use. It consists of a sterile silicone catheter-type device for transcervical placement, and it is applied

with the patient in lithotomy under aseptic conditions (after cleaning the vagina and cervix with liquid chlorhexidine) and using a sterile vaginal speculum to obtain access to the cervix. First, the mouldable stylet is adjusted so that its distal tip is at the height of the balloon, the tip is fixed, and the handle is firmly seated. The stylet is passed through the cervix and when the uterine balloon is positioned above the level of the internal cervical os, the stylet is withdrawn before advancing the catheter further. The double balloon is advanced until both balloons have been introduced into the cervical canal. The first balloon is inflated with 40 mL of sterile saline solution through the red valve (letter 'U'). The device is pulled back until the balloon is against the internal cervical os. The second balloon that remains outside the external cervical os is inflated with 20 mL of saline through the green valve (letter 'V'). The speculum is removed. Later, more liquid can be added up to a maximum of 80 mL in each balloon. The proximal end of the catheter can (optionally) be fixed to the patient's thigh with an adhesive strip, without pulling. It is kept in situ until its spontaneous expulsion or until 12 hours have passed since its insertion. If the catheter cannot be placed with a speculum, digitally guided placement can be attempted. If, despite this, the cervix is closed and it is not possible to introduce the catheter, the patient can be offered the possibility to return in 24–48 hours to make a second attempt. If despite this it is not possible to insert or if at any time the patient does not tolerate the procedure and does not wish to continue, induction with dinoprostone will be proposed.

2. Control arm (pharmacological method): Propess 10 mg vaginal delivery system is intended to use for cervical ripening. It consists of a non-biodegradable polymeric drug delivery device containing 10 mg dinoprostone (Prostaglandin E2) within the matrix. In the presence of humidity, it swells and releases dinoprostone in a sustained manner. It is placed in the posterior fornix of the vagina (behind the cervix) and the attached tape is allowed to protrude from the vagina to ensure easy removal. It remains in situ until 24 hours after insertion or cervical ripening has been achieved (Bishop score ≥7).

The cervical ripening method is always inserted by a member of the research team appropriately trained (experience of >50 previous insertions).

Follow-up

The maximum time of use of the different induction methods is that recommended by the manufacturers (12 hours for the Cook's balloon and 24 hours for dinoprostone). Despite this lack of coincidence in maximum times, the action of dinoprostone is not slower,[19] so we believe that it is still of interest to compare temporal outcomes between both methods, including the time from induction to delivery. The cervical ripening method may be removed before cervical ripening is complete (Bishop score ≥7) or before the maximum use time has passed since its insertion in the following circumstances: (1) tachysystole with alteration of the fetal tracing of the cardiotocography (CTG); (2) premature rupture of membranes during the insertion of the cervical ripening method or during the period in which they remain inserted (12 hours for the Cook balloon and 24 hours for dinoprostone) and (3) expulsion from the vagina in the case of Cook's balloon (in the case of dinoprostone, a new device will be placed). This will not imply the withdrawal of the patient from the study.

Apart from the cervical ripening method, there are no restrictions for the application of the conventional protocols followed in delivery rooms for maternal and fetal treatment and monitoring during the labour induction and delivery process. This includes the use of continuous CTG (external as first choice), artificial amniorrhexis, oxytocic infusion and intravenous fluids and analgesic methods such as epidural, intradural and pudendal block or nitric oxide inhalation. In general terms, amniotomy, followed by intravenous oxytocin administration, is performed within 1 hour of withdrawal of the cervical ripening method. In the case of dinoprostone, not before 30 min from its removal. Standardised infusion regimen of oxytocin is used (starting dose of 1mU/min, incremental increase of 1mU/min each 20–30 min and maximum dose of 40 mU/min), pursuing the minimum effective dose. This can vary due to different circumstances. For example, if the fetal presentation is high or there is a risk of vertical transmission of infection, starting oxytocin and delaying amniotomy may be considered. Also, if the mother presents sufficient spontaneous contractions for the progression of labour, the initiation or continuation of oxytocin may not be necessary.

The use of any other treatment necessary to control uterine hyperdynamia (ritodrine), fever (antipyretics and antibiotics) or hypertension (antihypertensives) is also permitted, as well as the administration of any medication that the patient requires during the study period for the treatment of any previous illness. There are also no relevant instructions for the postpartum period. A flow chart of the study is provided in figure 1.

Strategies to improve adherence to interventions

Adherence is favoured by the study design itself, as it is carried out during a single short hospital period and the administration of the cervical ripening methods is provided by trained researchers. In addition, researchers will be involved in promoting adherence to treatment, taking extreme care in the communication with the patients and their partners. Therefore, adequate time will be spent explaining the importance of randomisation and adherence, as well as assessing understanding before obtaining informed consent. The benefit of recruitment will be balanced against the risk of recruiting a patient who offers reasonable doubts about adherence. After enrolment, positive relationships between participants

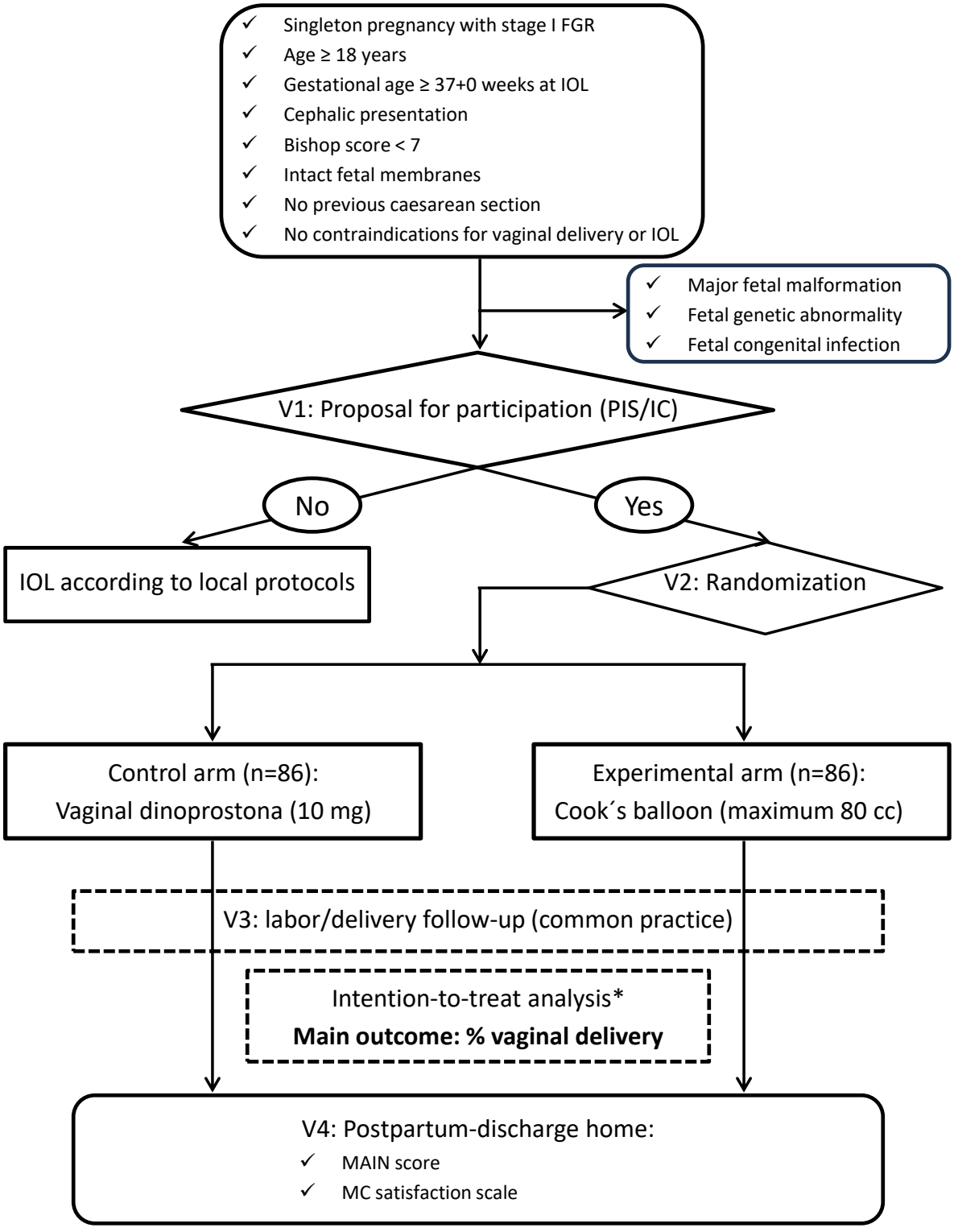

Figure 1 Trial flow diagram summarising the study design and the expected number of participants. *Primary analysis, including all patients randomised according to the assigned arm. Additional secondary analyses will be performed: safety analysis in those receiving any intervention and a per-protocol analysis in those who comply with the study protocol. FGR, fetal growth restriction; IOL, induction of labour; MAIN, morbidity assessment index for newborns; MC, Mackey childbirth; PIS/IC, patient information sheet/informed consent.

and the research team will be facilitated to promote collaboration in research.

Outcomes

1. Main outcome:
   - Vaginal delivery; binary (yes/no).
2. Secondary outcomes:
   - Vaginal delivery within 24 hours; binary (yes/no).
   - Emergent caesarean section for fetal distress; binary (yes/no).
   - Failed induction of labour (defined as the inability to achieve the active phase of labour, ie, a cervical dilation of at least 4 cm and 90% effacement or 5 cm regardless of effacement and regular contractions[20]); binary (yes/no).
   - Time from induction of labour to active labour; continuous (hours).
   - Total duration from induction of labour to delivery; continuous (hours).
   - Hyperstimulation (>5 contractions/10 min with CTG alteration[21] during the latent phase of labour; binary (yes/no).
   - Hyperstimulation during the active phase and second stage of labour; binary (yes/no).
   - Suspected intrapartum infection (maternal axillary temperature ≥37.8°C on two consecutive readings); binary (yes/no).
   - Neonatal morbidity: shoulder dystocia, neonatal acidosis (arterial cord pH <7.10 or base excess >12 mEq/L), NICU admission, hypoxic-ischaemic encephalopathy, meconium aspiration syndrome, sepsis, death (intrapartum, neonatal); all binary (yes/no). MAIN score of neonatal morbidity; ordinal scale. Days in NICU; continuous.
   - Severe maternal morbidity: haemorrhage requiring blood transfusion, uterine rupture, anal sphincter injury grade ≥3, deep vein thrombosis, postpartum septicaemia (maternal axillary temperature ≥37.8°C on two consecutive readings and evidence of urinary infection or endometritis demonstrated by a positive culture in the first week post partum), admission to intensive care unit, death; all binary (yes/no). The time frame for recording these outcomes will be from the inclusion in the study until the postpartum hospital discharge of the mother.
   - Maternal satisfaction: assessed with a short questionnaire about the childbirth experience: the Mackey childbirth satisfaction rating scale in its validated version in Spanish[13]; ordinal scale. The questionnaire will be administered between 24 hours after childbirth and hospital discharge of the mother.

Our primary outcome (vaginal delivery) has been chosen because it is the main result that is pursued with the induction of labour and provides advantages that are especially beneficial for newborns with FGR such as promoting early skin-to-skin contact and successful breast feeding, as previously explained. Secondary outcomes have been adapted from those recommended by experts[22] and those of interest for the analysis of mechanical methods.[19] In addition, we have added the outcome of 'Emergent caesarean section for fetal distress' as we speculate that it may be an important cause of caesarean section in labour induction when FGR is present.[12]

Control variables

They have been selected following the consensus criteria on the minimum variables to be reported in studies on FGR,[23] and are grouped as follows:

1. Maternal characteristics: age at delivery (years), parity (number of deliveries ≥22+0 weeks), pregestational weight (kg); height (cm), body mass index (kg/m^2), self-perceived ethnic origin (white/Caucasian, Hispanic, North-African, Asian, black or African-American, other), educational level, obstetric formula, method of conception (spontaneous, artificial insemination, in vitro fertilisation, ovodonation), substance abuse during pregnancy (smoking, alcohol, other drugs), history of pre-eclampsia, history of fetal smallness/growth restriction, history of chronic disease (hypertension, diabetes mellitus, renal disease, thrombophilia, systemic lupus erythematosus), aspirin prophylaxis, heparin prophylaxis or treatment.
2. Prenatal care: prenatal genetic testing performed (none, cell-free DNA, quantitative fluorescence PCR, karyotype, array-CGH), hypertensive disorders of pregnancy,[24] mean blood pressure at inclusion, use of corticoids for fetal maturation, gestational age at diagnosis of FGR.
3. Ultrasound findings (last week before induction): gestational age at ultrasound, EFW (g) according to Hadlock's formula[15] and percentile,[16] amniotic fluid deepest pocket (mm), Doppler study: pulsatility index in the umbilical artery, cerebral middle artery and uterine arteries and CPR (absolute values and percentile according to gestational age).[17 18 25]
4. Labour induction and delivery: gestational age and Bishop score at randomisation/start of labour induction, Cook's balloon catheter insertion failure, use and duration of neuraxial analgesia, use and duration of oxytocin, use of antibiotics during induction/labour (other than intrapartum antibiotic prophylaxis against Group B Streptococcus) mode of delivery (vaginal delivery, instrumental vaginal delivery, caesarean section), gestational age at delivery, birth weight (g) and percentile,[16] newborn sex, 5 min Apgar score, duration of postpartum maternal admission (days from birth to hospital discharge).

Participant timeline

The follow-up of the patients in this study consists of three phases. The first (phase 1: pretreatment) is carried out before hospital admission to verify compliance with the inclusion criteria and delivery scheduling. In the next two, the patient is admitted for induction of labour (phase 2: treatment) and monitoring of labour/delivery and postpartum (phase 3: post-treatment). Therefore, phase 1 and

Table 1 Participant timeline for the COLIGROW study

Phase	Pretreatment	Treatment	Post-treatment	
Visit	V1 (selection)	V2 (randomisation and IOL)	V3 (labour/delivery follow-up)	V4 (postpartum discharge home)
Time point (days)	−7 to −1	1–2	3±2	5±2
PIS/IC	X			
Inclusion/exclusion criteria	X			
Maternal characteristics	X			
Exploration:				
Blood pressure				
Bishop test	X	X (prerandomisation)		
Rule out PROM				
Ultrasound (biometry and Doppler)	X			
IOL programming	X			
Hospital admission		X		
Randomisation		X		
Cervical ripening		X		
Labour and delivery care			X	
Data collection (IOL, labour and delivery)				
Failed IOL		X		
Mode of delivery			X	
Duration of latent phase and labour		X	X	
Hyperstimulation		X	X	
Suspected intrapartum infection		X	X	
Neonatal morbidity (MAIN score)			X	X
Satisfaction (Mackey scale)				X
Maternal complications and adverse events	X	X	X	X

IOL, induction of labour; MAIN, morbidity assessment index for newborns; PROM, premature rupture of membranes; PIS/IC, patient information sheet/informed consent.

phase 2 consist of one visit each, while phase 3 consists of two visits (one at labour/delivery and one during the postpartum period). The maximum duration of patient treatment is 1 day. The follow-up period for each patient will last as long as the patient is hospitalised. Labour and delivery is expected to take place between days 2 and 3. Normally, postpartum follow-up is carried out from days 3 to 5. In the event that hospital stay is extended because of any circumstance, visit 3 will be extended for the entire time until hospital discharge. The participant timeline is shown in table 1.

Duration of the study

The estimated recruitment period is 26 months. Analysis of results, preparation of the final report and publication of results will take approximately 4 months. Overall, we plan a study duration of 2.5 years.

Sample size

The sample size needed to evaluate that cervical ripening with Cook's balloon for induction of labour at term in singleton pregnancies with stage I FGR achieves an increased probability of vaginal delivery compared with the use of vaginal dinoprostone, was calculated assuming that the vaginal delivery rate was 84.5% with mechanical methods vs 62.3% with prostaglandins (reported effect size: relative risk of 1.4, 95% CI 1.1 to 1.6 and absolute risk reduction of caesarean section of 22.2%).[12] In a one-sided test (H1) with early stopping to reject or accept H0 at an alpha level of 0.025 and statistical power of 90% with two-stage sequential design using the O'Brien-Fleming method, with 1:1 allocation to treatment, a total of 162 participants are required, 81 in each group. Due to possible losses, the sample is increased by 5% and consists of a total of 172 pregnant women, 86 in each group.

The programming code and the result are provided in the statistical analysis plan provided in online supplemental material.

Data analysis plan

1. Allocation:
   A randomisation list has been generated using SAS V.9 for Windows software (SAS Institute). Patients who meet the selection criteria are randomised in a 1:1 ratio between the two research groups in blocks of 6, stratifying by centre in order to achieve balanced randomisation in the two research groups. The assignment of treatment to each patient is centralised, keeping the sequence hidden.
2. Data collection:
   An electronic case report form (eCRF) has been created using the Research Electronic Data Capture management platform (V.14.2.1, Vanderbilt University) hosted by Instituto de Investigación Hospital 12 de Octubre (imas12). This is a secure web-based software platform for managing online databases that also provides automated data export to common statistical packages (including SAS).[26] Anonymised participant data are entered into the eCRF. Data access will be restricted to authorised personnel (investigators, monitors and regulatory health authorities) in charge of collecting and verifying the data with appropriate confidentiality. All clinical trial data generated by a site will be available to the local investigators at all times during and after the trial, and principal investigators will have access to other sites' data by request. When the collection and review of the study data are finally completed all electronic or paper documentation will be sent to the trial sponsor. The sponsor will retain the datafile for at least 25 years after the end of the trial. Data for the final statistical analysis will be transferred only once the database is locked. The data manager will prepare a file in SAS with the data ensuring that statistical analyses of the study data will be performed in a blinded manner by a third party to limit possible evaluation bias. Patients' information will be managed in accordance with European Regulation 2016/679 and Spanish legislation. Additional details are provided in the data management plan, included in online supplemental material.
3. Analysis population:
   The efficacy analysis will be performed in the intention-to-treat population. All randomised patients will be included in the intention-to-treat analysis and will be classified according to the assigned treatment group, regardless of the treatment received and whether they have received it.
   All pregnant women who receive at least 1 dose of the study intervention, that is, in whom one of the cervical ripening methods has been inserted, will be included in the safety analysis.
   The per-protocol population is considered to be all pregnant women who receive at least one dose of the assigned study treatment, complying with the protocol criteria (inclusion/exclusion) and following the instructions of the trial protocol. That is pregnant women who have been included in the study and have not incurred major deviations from the protocol during the study.
4. Statistical analysis:
   a. General considerations:
      At the end of the study, descriptive summaries of the demographic variables and other characteristics of the subjects specified in eCRD will be made based on the two treatment groups. Subgroup analysis is not contemplated. Unless otherwise specified, all continuous variables will be summarised using the number of patients (n), mean, SD, median, minimum and maximum. If the normality test (Kolmogorov-Smirnov test) is rejected, they will be described using the median together with the 25th and 75th percentile. Categorical variables will be described by absolute and relative frequency. No imputation procedure will be carried out on the study variables, although the origin of the missing data will be studied in relation to the follow-up of the patients and their evolution. The missing information in the objective variables will be quantified in absolute frequency and shown with respect to the total number of subjects per treatment arm. All analyses will be carried out using SAS V.9 for Windows software.
   b. Analysis of primary and secondary objectives:
      To evaluate that cervical ripening with Cook's balloon obtains a higher rate of vaginal deliveries than ripening with vaginal dinoprostone, a unilateral test (one-tailed test) of the χ^2 and alpha error equal to 0.025 will be carried out. The 95% CI of the difference in proportions will also be provided.
      Analysis of the secondary objectives will be carried out through the two-tailed χ^2 test and alpha error equal to 0.05 or the Fisher's exact test for categorical variables (rates of caesarean sections due to suspected fetal distress, neonatal acidosis and admission to the NICU) between the two groups.
      The evaluation of the meantime interval between the onset of cervical ripening and delivery and the MAIN score of neonatal morbidity between groups will be assessed through a two-tailed t-test and alpha error equal to 0.05. If the normality hypothesis is rejected (Kolmogorv-Smirnov test), a Mann-Whitney-Wilcoxon test will be performed for two samples.
5. Interim analysis plan:
   A sequential design will be used to stop the trial early for the effectiveness of cervical ripening with Cook's balloon on the rate of vaginal birth versus the rate of vaginal birth with vaginal dinoprostone cervical ripening. The sequential design will use the O'Brien-Fleming method for two stages, with a starting alpha

level equal to 0.025 and will use a unilateral alternative hypothesis (H1) with an early stop to reject or accept the null hypothesis (H0). The first stage will be carried out when the study is completed in 88 pregnant women, 44 in each branch, which will correspond approximately to 13 months, and will have the following scheme:

- If the Z statistic ≥2.767, then H0 is rejected, and the study is stopped.
- If Z statistic <0.437, then H0 is accepted, and the study is stopped.

In any other case, the study continues.The second stage will coincide with the end of the study (approximately 26 months), 172 pregnant women, 86 in each group. It will be evaluated as follows:

- If Z statistic ≥1.957, then H0 is rejected.
- If Z statistic <1.957, then H0 is accepted.

6. Data monitoring and safety:
Independent monitors from the SCReN platform are planned to audit the trial. Before recruitment begins, a site initiation visit is conducted at each centre to discuss the study plan, review the study documents and ensure that the study personnel are trained, and all investigators are aware of the appropriate reporting process in case of adverse events. Adverse events will be reported to regulatory authorities and the ethics committee within 1 week, or within 48 hours if they involve an imminent risk of death or serious injury. Two (or three if necessary) intermediate monitor visits are scheduled to independently verify the study data with the source documents as well as protocol adherence. After enrolment has been completed a site close-out visit will be conducted to ensure that all data are completed, and regulatory documents are on file. Further details of data management procedures are provided in the data management plan (online supplemental material).

Patient and public involvement

Patients and the public are not involved in the design and conduction of the trial, but participants will be involved in the interpretation and dissemination of the study results by providing their perspective and patient experience. Their contribution will be appropriately recognised.

ETHICS AND DISSEMINATION

The trial was registered in the European Union drug regulating authorities' clinical trials database (EUDRACT) (2021-001726-22) and later received approval from the local Ethics Committee (21/728) and the Spanish Agency of Medicines and Medical Devices (AEMPS). AEMPS classified the trial as a low-intervention trial, so it was not required to take out trial insurance. Enrolled patients are covered by indemnity for negligent harm through insurance contracted for this purpose by each participating hospital. The medical device under investigation, the Cook's balloon, will be used at the time of labour induction, so once the study is completed, no special healthcare is expected to be required. Patients will be followed according to the usual clinical practice of each of the participating centres. It is not planned to store data or biological samples for ancillary studies. Finally, the protocol was registered in ClinicalTrials.gov (ID: NCT05774236). The study is conducted in compliance with the principles of the most recent Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial protocol modification (such as changes to eligibility criteria, outcomes, analyses or inform consent) will be communicated by the sponsor to the local Research Ethics Committee and AEMPS for their evaluation and authorisation. Protocol modifications will not be effective until approved by such authorities, except for changes that are necessary to protect the patient or others from imminent risk.

The results of the COLIGROW study will be disseminated through workshops and national/international conferences and published in peer-reviewed journals. Authorship criteria for the publication of the results will follow the updated Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.[27] Employment of professional medical writers is not planned.

In addition, the results and conclusions will be disclosed to patients and the public in understandable language through study newsletters and press releases to news and social media.

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Correction notice This article has been corrected since it was first published. Affiliation 4 has been corrected.

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Acknowledgements The authors thank Carmen Romero and Cristina Martín-Arriscado for their contribution on the Statistical Analysis Plan. We also thank Cristina Justel from the SCReN platform, for her invaluable support.

Contributors IH is the project monitor and principal investigator, conceived the study and contributed to the designed data collection tools. IH is also the guarantor of the study and accepts full responsibility for the finished work. EMeler coordinates

the study and will participate in the implementation of the study (inclusion of women, randomisation, management of women during the study period and data coding) at her site. EMazarico coordinates the study and will participate in the implementation of the study at her site. EB coordinates the study and will participate in the implementation of the study at her site. JEB coordinates the study and will participate in the implementation of the study at his site. CV contributed to the designed data collection tools and will participate in the implementation of the study at her site. PB will participate in the implementation of the study at her site. AP will participate in the implementation of the study at her site. AB will participate in the implementation of the study at her site. MLS will participate in the implementation of the study at her site. ILM monitors data collection for the whole trial. DLP wrote the statistical analysis plan and will be responsible for analysing and reporting the data. FF contributed to the conception of the study and will participate in the implementation of the study at his site. AG contributed to the conception of the study and will participate in the implementation of the study at his site. All authors contributed to the design and writing of the study protocol and approved its final version. FF and AG equally contributed as last authors.

Funding This study has been funded by Instituto de Salud Carlos III (ISCIII) through the projects RD21/0012/0024 (Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin: RICORS network), PI19/01005 and PT20/00193 (SCReN) and co-funded by the European Union (European Regional Development Fund).

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 section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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