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Mechanical cervicAl ripeninG for women with PrOlongedPregnancies (MAGPOP): protocol for a randomised controlled trial of a silicone double balloon catheter versus the Propess system for the slow release of dinoprostone for cervical ripening of prolonged pregnancies

Caroline Diguisto,[1,2] Amélie Le Gouge,[3] Bruno Giraudeau,[2,3] Franck Perrotin[1,2]

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[1]Maternité Olympe de Gouges, Centre Hospitalier Régional Universitaire Tours, Tonnellé, France
[2]Université François Rabelais Tours, Tonnellé, France
[3]INSERM CIC 1415, CHRU de Tours, Tours, France

Correspondence to
Dr Caroline Diguisto;
carolinediguisto@gmail.com

ABSTRACT

Introduction Induction of labour for prolonged pregnancies (PP) when the cervix is unfavourable is a challenging situation. Cervical ripening by pharmacological or mechanical techniques before oxytocin administration is used to increase the likelihood of vaginal delivery. Both techniques are equally effective in achieving vaginal delivery but excessive uterine activity, which induces fetal heart rate (FHR) anomalies, is more frequent after the pharmacological intervention. We hypothesised that mechanical cervical ripening could reduce the caesarean rate for non-reassuring FHR especially in PP where fetuses are already susceptible to this.

Methods and analysis A multicentre, superiority, open-label, parallel-group, randomised controlled trial that aims to compare cervical ripening with a mechanical device (Cervical Ripening Balloon, Cook-Medical Europe, Ireland) inserted in standardised manner for 24 hours to pharmacological cervical ripening (Propess system for slow release system of 10 mg of dinoprostone, Ferring SAS, France) before oxytocin administration. Women (n=1220) will be randomised in a 1:1 ratio in 15 French units. Participants will be women with a singleton pregnancy, a vertex presentation, a term ≥41+0 and≤42+0 week's gestation, and for whom induction of labour is planned. Women with a Bishop score ≥6, a prior caesarean delivery, premature rupture of membranes or with any contraindication for vaginal delivery will be excluded. The primary endpoint is the caesarean rate for non-reassuring FHR. Secondary outcomes are related to delivery and perinatal morbidity. As study investigators and patients cannot be masked to treatment assignment, to compensate for the absence of blinding, an independent endpoint adjudication committee, blinded to group allocation, will determine whether the caesarean for non-reassuring FHR was justified.

Ethics and dissemination Written informed consent will be obtained from all participants. The Tours Research ethics committee has approved this study (2016-R23, 29 November 2016). Study findings will be submitted for publication and presented at relevant conferences.

Trial registration number NCT02907060; pre-results.

Strengths and limitations of this study

- Mechanical cervicAl ripeninG for women with PrOlongedPregnancies is the first multicentre randomised controlled trial to compare mechanical cervical ripening to pharmacological cervical ripening among women with prolonged pregnancies.
- Physicians and patients cannot be blinded to treatment.
- To reduce the risk of bias, we chose for the primary outcome the rate of caesarean for non-reassuring fetal heart rate which is an objectively measured outcome that is nonetheless potentially influenced by clinicians.
- These limitations are compensated by the independent adjudication committee, which will adjudicate the indication of caesarean and be blinded to the method of cervical ripening.

INTRODUCTION

Pregnancies that reach 41 weeks of gestation are considered to be prolonged. They account for 15% of pregnancies and are associated with increased perinatal morbidity.[1] The risks include more fetal heart rate (FHR) anomalies and a higher risk of fetal asphyxia during labour.[2 3] To reduce this morbidity, induction of labour is recommended from 41 weeks of gestation in many countries.[4–6]

When the cervix is unfavourable, such induction is challenging; cervical ripening before oxytocin administration increases the likelihood of vaginal delivery.[7] Various ripening methods are available; they include pharmacological options, mainly dinoprostone (prostaglandin E2), as well as mechanical methods (a Foley catheter or silicone double balloon catheter).[8] Although both methods have proved effective in achieving vaginal deliveries in term pregnancies, both uterine hyperstimulation causing FHR anomalies and neonatal intensive care admissions are more frequent after pharmacological compared with mechanical ripening.[8–11] The association of FHR anomalies (ie, non-reassuring FHR: suspicion of fetal asphyxia) with pharmacological methods suggests that the latter may not be the most appropriate method in cases of prolonged pregnancies (PP) as these fetuses are already at a higher risk of asphyxia. No particular method is currently recommended for cervical ripening in PP and practices vary.[12 13] We hypothesise that mechanical cervical ripening, which involves less excessive uterine activity, which in turn causes FHR anomalies, could reduce the rates of both caesarean sections for non-reassuring FHR and perinatal morbidity in PP.

METHODS AND ANALYSIS

Study design

Mechanical cervicAl ripeninG for women with PrOlonged-Pregnancies (MAGPOP) is a multicentre, superiority, open-label, randomised controlled trial with two parallel groups comparing mechanical cervical ripening to pharmacological cervical ripening among women with PP.

Setting

The study will take place in 15 French maternity units in both university and general hospitals, each with >2000 deliveries annually. Inclusions will start in January 2017. All maternity units are equipped with maternal and neonatal intensive care units. Obstetricians in all maternity units are familiar with and use both cervical ripening techniques (as described in the intervention section below) in their daily practice.

Participants

Study population

The inclusion criteria are (1) women≥18 years; (2) pregnant with a singleton pregnancy, a vertex presentation with a term ≥41+0 and≤42+0 weeks of gestation (gestational age estimated from an ultrasound performed between 11 and 13+6 weeks of gestation); and (3) for whom induction of labour has been decided. The exclusion criteria are Bishop score ≥6 (favourable cervix), a non-vertex presentation (breech or transverse), severe pre-eclampsia, previous caesarean delivery or other uterine scar, placenta praevia, suspected genital herpes infection, known HIV seropositivity, premature rupture of membranes with either continual leaking of or a test result positive for amniotic fluid, suspected severe congenital abnormalities and a pathological FHR. The study will include the women who meet all inclusion criteria and no exclusion criteria and who are willing to participate and able to sign informed consent.

Recruitment

French guidelines call for monitoring of fetal well-being every other day in PP.[5] This surveillance period is monitored by midwives, sonographers and physicians, who will recruit potential participants by screening women and describing the study objectives to those who meet the inclusion criteria. Because some women are likely to go into labour spontaneously and the Bishop score is likely to change during uterine contractions, randomisation should take place just before cervical ripening is planned to begin.

On the day that cervical ripening is planned, examination will include verification of all inclusion and exclusion criteria. Cervical examination will determine the Bishop score, and fetal cardiotocography will verify the normality of FHR according to FIGO's revised classification.[14] Written consent will be obtained from all women who meet all inclusion and no exclusion criteria, have been fully informed about the study and are willing to participate.

Randomisation

Participants will be randomly allocated in a 1:1 ratio to one of the two treatment groups.

Randomisation and concealment will be ensured by a secure, computer-generated, online centralised web-based system. Randomisation will be stratified on centre (to avoid measurement biases) and parity (to avoid prognostic imbalance between the groups).

The randomisation sequence will be generated by a statistician from INSERM CIC 1415 who is not involved in patient recruitment.

Interventions

Women admitted for cervical ripening will be fasting. Only the method used for cervical ripening (silicone double balloon catheter or the slow-release system) will differ between the two groups. Midwives or medical doctors (senior and junior) are responsible for placement of the silicone double balloon catheter or the dinoprostone slow-release system. Both placements are simple procedures.

Mechanical cervical ripening

The mechanical cervical ripening device is a silicone double balloon catheter with an adjustable length malleable stylet (Cook Cervical Ripening Balloon, Cook Medical Europe, Limerick, Ireland, reference J-CRBS-184000), which will be inserted according to the manufacturer's recommendations.[15]

The aim is to position the upper or uterine balloon against the internal os and the lower balloon in the vagina so that the catheter is in the cervical canal. Inflation of both balloons induces pressure against the cervix,

intended to induce the release of prostaglandins and thus uterine contractions.

The first step consists in inserting the malleable stylet into the silicone catheter, stiffening the catheter and facilitating the catheter's introduction into the cervix. The patient should be in the gynaecological position. A speculum is first inserted to gain cervical access, and the cervix wiped with an appropriate (according to the woman's allergies) solution to prepare for device insertion. The catheter is introduced into the cervical canal so that both balloons reach the extra-amniotic space. Clinicians first inflate the upper (uterine) balloon with 40 mL of saline. Once the upper balloon is inflated, the operator pulls the device back until the balloon abuts the internal cervical os. The vaginal balloon is then visible outside the external cervical os and is next inflated with 40 mL of saline. Once the balloons are situated on either side of the cervix, saline is inserted in both balloons to a maximum volume of 80 mL per balloon.

Pharmacological cervical ripening

The pharmacological cervical ripening procedure is the administration of a system for the slow vaginal release of 10 mg dinoprostone (prostaglandins PGE2 Propess, Ferring SAS, Gentilly, France). The Propess slow-release system is inserted in the vagina, against the cervix, with or without a speculum, according to the local protocol.

Intervention standardisation

Volunteer maternity units were selected to participate only if they regularly used both techniques (catheters and slow-release system) so that all physicians and midwives responsible for inserting the devices were accustomed to using both options in their daily practice. An information meeting was held in each participating unit to verify that both devices were used according to guidelines and to ensure homogeneity of practices.

To ensure the absence of bias induced by the product management, the investigator's pharmacy will supply all devices in each investigational site. Pharmacists at each investigational site are responsible for traceability and storage: the silicone double balloon catheters must be stored in a dry place, away from light, and the slow-release systems in a freezer at −20°C to −10°C.

Follow-up

After cervical ripening begins, women in both groups will be monitored identically. FHR will be monitored by external tocography for 2 hours, as French guidelines recommend.[7] If labour is not induced immediately and if the FHR is reassuring, fetal condition and uterine activity will be intermittently monitored, as recommended.[7] If premature rupture of the membranes or FHR anomalies occur, the devices (either the catheter or the dinoprostone slow-release system) should be removed. If FHR anomalies persist, and uterine hyperactivity appears to be the cause of these anomalies, tocolysis can be considered.

Should the catheter be expelled, a new catheter should not be inserted: because expulsion indicates that the cervix is at least two centimetres dilated, the Bishop score is high enough to proceed to oxytocin administration. Because dinoprostone is not effective until at least 12 hours after placement, expulsion of the system (the loss rate is expected to be 5%) during the first 12 hours should be followed by insertion of a new one, but expulsion after 12 hours should not. If labour starts at any time, the patient will be transferred to the labour ward. Epidural analgesia will be placed according to the patient's wishes and the usual medical indications and contraindications.

If labour has not started by 24 hours after cervical ripening began, the device (catheter and slow-release system) should be removed to start the induction of labour with oxytocin/amniotomy. As recommended, perfusion of oxytocin should not start until at least 30 min after device removal.[7]

Blinding

The nature of the intervention makes it impossible to blind any of the physicians, midwives or women. Measures will be taken to compensate for the absence of blinding (see below 'adjudication committee').

Study outcomes

Primary outcome

We have chosen not to use either the caesarean rate or the rate of vaginal delivery at 24 hours as principal endpoints, despite their frequent use for this purpose in clinical research, because it has already been proved that mechanical and pharmacological techniques are equally effective for these outcomes.[10] Our hypothesis instead is that mechanical ripening can reduce caesarean sections for non-reassuring fetal status in PP fetuses, who are more vulnerable to this outcome. Accordingly, the primary endpoint is the caesarean rate for non-reassuring fetal status (with or without arrest of labour) and it will be determined by an adjudication committee.

Adjudication committee

Although caesarean delivery is an objective outcome, the decision to perform a caesarean is not. Two different physicians may take different decisions for the same obstetric situation, and physicians frequently disagree about indications for caesareans. Similarly, the same physician facing the same situation twice may decide differently each time. Our primary outcome is considered to be an outcome 'objectively measured but potentially influenced by clinician judgment', as defined by Savovic *et al*.[16] To avoid bias due to this physician influence on outcome, we decided that a blinded independent committee would adjudicate the primary outcome at the end of the study. This committee will comprise three members, all with extensive experience in interpreting FHR and none working in a participating centre. Once inclusion is complete and all the data have been collected, the committee will adjudicate all primary outcomes, blinded to the method of

cervical ripening, determining whether or not non-reassuring fetal status indicated/justified the caesarean. This is therefore a PROBE study: Prospective, Randomised, Open, with Blinded Evaluation.

Secondary outcomes

Secondary outcomes include the following.

Outcomes related to delivery

Time between cervical ripening and delivery in hours, delivery rate after 12 and 24 hours of cervical ripening, need for induction with oxytocin, total dose of oxytocin before delivery, uterine hyperstimulation defined as more than six contractions per 10 min over any 30 min period, need for tocolysis, suspicious or pathological FHR, uterine rupture and use of analgesics and antibiotics. In cases of caesarean delivery, caesarean deliveries for non-reassuring fetal status (as defined by investigators), indications for caesarean delivery other than non-reassuring FHR will be reported (failure to progress in the first or second stage of labour or maternal indication). In cases of vaginal delivery, instrumental delivery (and its indication) will be reported.

Outcomes related to maternal morbidity

Maternal fever during labour, suspected maternal intrapartum or postpartum infection, postpartum haemorrhage defined as estimated blood loss >500 mL, blood transfusion, perineal complications, death, admission to intensive care, thromboembolic complications and length of hospitalisation. In cases of wound infection or haematoma after caesarean delivery, need for prolonged wound care will be reported.

Outcomes related to neonatal morbidity

Neonatal death, Apgar score, arterial and venous pH at delivery, need for resuscitation at birth, admission to a neonatal unit or an intensive care unit and length of hospitalisation, suspected neonatal infection, respiratory insufficiency with need for any respiratory support and neonatal asphyxia.

Sample size calculation

The sample size was calculated from data obtained from the NOCETER trial, which took place in 11 French maternity units and evaluated cervical ripening among women with PP and a Bishop score <6.[12] It finally reported a caesarean rate of 27%; 17.7% of the treatment group had caesareans for non-reassuring FHR. Accordingly, we hypothesise that the caesarean rate for fetal distress will be 17.7% in the pharmacological group and that mechanical cervical ripening will reduce the rate to 12%. To detect a reduction from 17.7% to 12% of the main outcome (caesarean for non-reassuring FHR) with a power of 80% and a two-tailed type I error of 5%, we need to include a total of 1220 women (610 in each group).

Data collection

Data will be collected from the medical records by clinical research assistants and anonymised. An online, secure, centralised web-based system will be used to collect all baseline characteristics and all the outcomes mentioned above. The FHR monitoring for 2 hours before all caesarean deliveries and all vaginal deliveries complicated by neonatal asphyxia (defined by arterial pH <7.00, a base excess >12 mmol/L and encephalopathy) will be collected.

Statistical analysis

Statistical analysis will be performed according to the intention-to-treat principle: each patient will remain in the group to which she was assigned by randomisation, regardless of subsequent events. A statistical report will be written according to CONSORT statement recommendations for non-pharmacological treatment interventions. Baseline characteristics will be reported per group with descriptive statistics and no statistical tests.

Primary endpoint

The rate of caesarean sections performed for non-reassuring fetal status will be reported as the point estimate with its 95% CI for each group and will be compared with the χ^2 test.

Secondary endpoints

The rates of outcomes will be compared with χ^2 or Fisher's exact test for qualitative data and by the Student's or Kruskal-Wallis test for quantitative data. Statistical analysis will be performed with SAS V.9.2 and R V.2.15.0 (or later versions) software.

Ethics and dissemination

The study protocol (see online supplementary file) and patient information documents were approved by the competent French authorities (Agence Nationale de Sécurité du Médicament et des produits de santé and Comité de Protection des Personnes de TOURS - Region Centre ; 2016-R23, 29 November 2016).

The study protocol is registered at ClinicalTrials.gov (NCT02907060) and in the European EudraCT database (2016-A00952-49). After receiving information about the study from a physician or midwife, all participants will sign a written informed consent form.

Research findings will be reported at ClinicalTrials.gov and submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. The study findings will also be presented at relevant national and international obstetrics conferences.

DISCUSSION

MAGPOP is the first multicentre superiority, open-label, randomised controlled trial with parallel groups to compare a silicone double balloon catheter to a system

for slow release of vaginal dinoprostone in PP, a situation in which fetuses are more prone to asphyxia because of defective placental function. Mechanical ripening may be a safer procedure than pharmacological ripening in these situations.

Our ultimate aim, if our hypothesis is confirmed, will be to assess extension of the use of mechanical methods to situations of 'fragile or compromised fetuses' besides PP, such as small-for-gestational-age fetuses or those with indicated preterm delivery. The aim is to reduce the caesarean rates for these births. Around 20% of deliveries in France are caesarean sections. This mode of delivery, which is inevitable in some situations, considerably increases perinatal morbidity and is a major public health issue.[17–19] Caesarean deliveries are associated with longer hospitalisation of women, thromboembolic risk, postoperative wound infection, global cost of care and long-term outcome (increased risk in subsequent pregnancies of, eg, placenta percreta). Reducing the caesarean rate would also improve neonatal health by reducing the risk of neonatal respiratory distress, admission to the neonatal ward and neonatal mortality. Limitations of this study include the impossibility of blinding and the choice of an objectively measured outcome that is nonetheless potentially influenced by clinicians. These limitations are compensated by the independent adjudication committee, which will be blinded to the method of cervical ripening.

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Contributors CD, FP, ALG and BG conceived and designed the trial. CD and FP wrote the manuscript. FP and CD will be the principal investigators and will recruit patients and conduct the trial. ALG and BG planned the statistical analysis. All authors have read and approved the final manuscript.

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Competing interests None declared.

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