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ABSTRACT

Introduction It remains uncertain whether the most appropriate management for women with an unfavourable cervix after 24 hours of cervical ripening is repeating the ripening procedure or proceeding directly to induction by oxytocin. No adequately powered trial has compared these strategies. We hypothesise that induction of labour with oxytocin among women who have just undergone an ineffective first ripening procedure is not associated with a higher risk of caesarean delivery than a repeated cervical ripening with prostaglandins.

Methods and analysis We will conduct a multicentre, non-inferiority, open-label, randomised controlled trial aimed at comparing labour induction by oxytocin with a second cervical ripening that uses prostaglandins (slow-release vaginal dinoprostone; oral misoprostol 25 µg; dinoprostone vaginal gel 2 mg). Women (n=1494) randomised in a 1:1 ratio in 10 French maternity units must be ≥18 years with a singleton fetus in vertex presentation, at a term from ≥37+0 weeks of gestation, and have just completed a 24-hour cervical ripening procedure by any method (pharmacological or mechanical) with a Bishop score ≤6. Exclusion criteria comprise being in labour, having more than 3 contractions per 10 min, or a prior caesarean delivery or a history of uterine surgery, or a fetus with antenatally suspected severe congenital abnormalities or a non-reassuring fetal heart rate. The primary endpoint will be the caesarean delivery rate, regardless of indication. Secondary outcomes concern delivery, perinatal morbidity, maternal satisfaction and health economic evaluations. The nature of the assessed procedures prevents masking the study investigators and patients to group assignment.

Ethics and dissemination All participants will provide written informed consent. The ethics committee 'Comité de Protection des Personnes Ile de France VII' approved this study on 2 April 2021 (No 2021-000989-15). Study findings will be submitted for publication and presented at relevant conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ OPIC (Oxytocin versus prostaglandins for labour induction of women with an unfavourable cervix after 24 hours of cervical ripening) is the first high powered multicentre randomised controlled trial to compare labour induction by oxytocin with a second cervical ripening that uses prostaglandins.
⇒ It integrates with the obstetric outcomes both maternal satisfaction outcomes and economic considerations, neither previously included in this context.
⇒ Physicians and patients cannot be blinded to treatment.
⇒ We chose an objectively measured primary outcome: the rate of caesarean delivery, regardless of indication.

Trial registration number NCT04949633.

INTRODUCTION

Approximately one in five births is induced worldwide.[1] Cervical ripening before oxytocin administration is advised in women with an unfavourable cervix to reduce the risk of caesarean delivery. After 24 hours of cervical ripening, most women will either have given birth or be in labour, but 15%–30% of those who undergo cervical ripening, regardless of the method, still have an unripe cervix.[2 3] There is no evidence about the best strategy in this situation. Both trials and national surveys set in different countries show that practices vary: some obstetricians perform a caesarean, some practitioners proceed to induction with oxytocin and others repeat cervical ripening,

sometimes for several days, until they obtain a favourable cervix or until amniotomy is feasible.[4 5] The latter consider that repeating the cervical ripening process might increase the likelihood of vaginal delivery,[3] but the vaginal delivery rate, perinatal morbidity, maternal satisfaction and costs of these repeated procedures have never been investigated by an adequately powered trial.[3 6]

We seek to identify the most appropriate strategy for managing women with an unfavourable cervix after 24 hours of cervical ripening, that is, the strategy associated with the lowest caesarean rate and the best maternal satisfaction. We hypothesise that induction of labour by oxytocin of women with an ineffective first ripening procedure is not associated with a higher risk of caesarean delivery than repeated cervical ripening with prostaglandins.

METHODS AND ANALYSIS

Study design

The OPIC trial (Oxytocin vs Prostaglandins for labour Induction of women with an unfavourable Cervix after 24 hours of cervical ripening) is a multicentre, non-inferiority, open-label, randomised controlled trial with two parallel groups comparing labour induction by oxytocin to a second cervical ripening procedure, with prostaglandins, in women with an unfavourable cervix (Bishop score ≤6) after 24 hours of cervical ripening by either a pharmaceutical or a mechanical process.

Setting

The study will take place in 10 French maternity units in both university and general hospitals, in which at least 2000 women deliver annually, all equipped with maternal and neonatal intensive care units.

Participants

The inclusion criteria are (1) pregnant women ≥18 years; (2) with a singleton fetus in vertex presentation at a term from ≥37+0 weeks (gestational age estimated by an ultrasound scan performed between 11 and 13+6 weeks of gestation); (3) who has just undergone a 24-hour cervical ripening procedure by any method (pharmacological or mechanical); (4) still has a Bishop score ≤6 (unfavourable cervix), when using all components of the Bishop score (a score of 0, 1 or 2 being assigned to cervical effacement, consistency, position and dilatation, and to the station of the presenting fetal part); (5) is French national health insurance holder (6) and has provided written informed consent (online supplemental file).

The exclusion criteria will be being in labour or having more than 3 contractions per 10 min, a previous caesarean delivery or a history of uterine surgery, any contraindications to prostaglandins, oxytocin, antenatally suspected severe congenital abnormalities, a non-reassuring fetal heart rate or the inability to provide legal consent. Ruptured membranes will not be an exclusion criterion.

Recruitment

Women who will require labour to be induced with cervical ripening will be informed of the study's objectives by midwives or physicians when induction is decided. Twenty-four hours after cervical ripening began, women who are not be in labour will have a cervical examination (determination of Bishop score) and fetal cardiotocography. Women will be included if they meet all inclusion and no exclusion criteria, have been fully informed about the study, are willing to participate, have signed the consent form (online supplemental file) and that the necessary room and treatment are available for both groups to avoid any measurement bias due to the per-protocol (PP) analysis.

Randomisation

Participants will be randomly allocated in a 1:1 ratio to one of the two treatment groups. Randomisation will be computer generated by a secure, online, centralised system—ENNOV CLINICAL. Randomisation, using permuted blocks of different sizes, will be stratified by centre (to avoid biases due to the variability of care between units) and parity (nulliparas vs others to avoid prognostic imbalance between the groups). The allocation sequence will be generated by a statistician from INSERM CIC 1415 who is not involved in the recruitment or follow-up of the participants.

Interventions

Women will receive the treatment allocated to their randomisation group.

Experimental group

Oxytocin will be stored in conditions meeting regulatory requirements, refrigerated at a controlled temperature (2°C–8°C). Women in the experimental group will be admitted to the labour ward to undergo induction of labour with intravenous oxytocin, administered according to the French guidelines (Haute Autorité de Santé, Recommandations 'Déclenchement artificial du travail à partir de 37 semaines d'aménorrhée' April 2008[7] with a maximum oxytocin dose ≤10 IU. The protocol for induction by oxytocin will be reviewed in a meeting planned at each recruiting centre before any inclusion. It will be recommended that each centre aim to use continuous fetal monitoring and the smallest amount of oxytocin necessary to obtain active labour, and to proceed to amniotomy as early as possible.

Control group

Women in the control group will undergo a second cervical ripening procedure that will last up to 24 hours. Investigators in each participating unit will choose only one ripening agent at the beginning of the trial according to the habits and protocols within their unit. The choice will be made between the following agents, all stored in conditions meeting regulatory requirements:

- A slow-release system of vaginal dinoprostone (PROPESS), inserted in the vagina against the cervix

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for 24 hours (stored at temperatures between −20°C and −10°C).
- Oral misoprostol (ANGUSTA), 25 µg every 2 hours, 8 times with maximum dosage not exceeding 200 µg (stored in a dry place at room temperature away from light).
- Dinoprostone vaginal gel (PROSTINE) 2 mg (stored at temperatures between 2°C and 8°C) to insert in the posterior fornix every 6 hours with a maximum dosage not to exceed 6 mg.

Midwives or obstetricians (junior or senior) will be responsible for placing the dinoprostone slow-release system and vaginal gel. Oral misoprostol will be given to women who will be advised to swallow the tablet with water.

Fetal heart rate will be monitored by external tocography for 2 hours after the beginning of the second ripening procedure, as French guidelines recommend. If labour does not start immediately and if the fetal heart ratio is reassuring, fetal condition and uterine activity will be monitored intermittently. The patient will be transferred to the labour ward as soon as labour starts. Twenty-four hours after this second ripening procedure began, women not in labour will be transferred to the labour ward for induction of labour with oxytocin regardless of cervical condition.

Follow-up

All ripening agents and procedures should be stopped when labour starts. Monitoring of oxytocin administration and labour will be identical in both groups. Epidural analgesia will be placed according to the patient's wishes, with the usual medical indications and contraindications. No particular instructions will be given for delivery and the postpartum period.

Blinding

The nature of the procedures makes the blinding of caregivers or women impossible as (1) the procedures are done in different places (intravenous oxytocin must be administered in the labour ward, while ripening usually takes place in the traditional antenatal ward); (2) the monitoring protocol is different (oxytocin administration requires full-time monitoring of the fetal heart rate and uterine activity whereas women from the control group only need intermittent monitoring); (3) the route of administration is different (intravenous for the intervention group and oral/vaginal for the control group) and (4) the durations of these procedures differ.

Study outcomes

Primary outcome

The primary outcome is the rate of caesarean delivery, regardless of its indication. To standardise practices as much as possible, the definitions of 'failed induction' and of 'arrest of labour' set forth in the ACOG/SMF (The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine) consensus statement[8] will be reviewed during the information meetings.

Secondary outcomes

Outcomes related to delivery

The secondary outcomes will include time from intervention to delivery, delivery within 12 hours, the indication for each caesarean performed (abnormal presentation, fetal compromise, maternal compromise, failure to progress in the first or the second stage of labour, failed induction, failed instrumental delivery), instrumental delivery and indication for the use of instruments (failure to progress or fetal compromise), need for induction with oxytocin (for women in the control group only), oxytocin augmentation, uterine hyperstimulation.

Outcomes related to maternal morbidity

Secondary outcomes will also include suspected intrapartum infection (defined as maternal temperature >38.5°C during ripening, labour or post partum), postpartum haemorrhage (defined as blood loss exceeding 500 mL in the 24 hours after delivery), severe postpartum haemorrhage (defined as blood loss exceeding 1000 mL in the 24 hours after delivery), blood transfusion during labour or in the postpartum period, anal sphincter injury at delivery (whether or not it affects the anorectal mucosa), need for antibiotics during ripening, labour or the postpartum period (other than antibiotics indicated for maternal carriage of group B Streptococcus), length of hospital stay, cardiorespiratory arrest, damage to internal organs, hysterectomy for any complications resulting from birth, pulmonary embolus, stroke, admission to an intensive care unit and maternal death.

Outcomes related to neonatal morbidity

Neonatal secondary outcomes will include the infant's admission to an intensive care unit, early neonatal infection defined by a positive bacteriologic sample in the first 72 hours after birth, neonatal acidosis defined as umbilical arterial pH<7.00 or a 5 min Apgar score <7, birth trauma, hypoxic ischaemic encephalopathy or need for therapeutic hypothermia, meconium aspiration syndrome, need for respiratory support, neonatal seizures and death of the baby.

Outcomes related to maternal satisfaction

Women's satisfaction will be assessed with the Questionnaire for Assessing Childbirth Experience (QACE), a short paper questionnaire for assessing the childbirth experience.[9] The paper questionnaire and a stamped envelope will be distributed to women the day they leave the unit. Women will be asked to complete the questionnaire 4 weeks after delivery and to send it back to the unit in the stamped envelope.

Outcomes related to health economic evaluation

In a joint analysis, the economic and clinical non-inferiority of inducing labour with oxytocin will be assessed in comparison with repeated cervical ripening.

Its probability of being clinically and economically non-inferior will be estimated for particular values of the clinical and economic non-inferiority margins.

Sample size calculation

The sample size was calculated from data obtained from a recent French prospective observational study conducted in 94 maternity units, showing that among women with an unfavourable cervix after 24 hours of cervical ripening, the caesarean delivery rate was 37%. Assuming a caesarean rate of 37% in each group and with a 7% non-inferiority margin, this individually randomised trial would require the inclusion of 1494 women to achieve a power of 80% (with a two-tailed type I error of 5%), that is, 747 women in each group.

Data collection

Data will be anonymously collected from the medical records by clinical research assistants. An online, secure, centralised web-based system will be used to collect all baseline characteristics and all outcomes mentioned above into a protocol-specific electronic case report form.

Statistical analysis

Statistical analysis will be performed, by someone who is blinded from the allocation group, according to the per protocol and intention-to-treat principles. A statistical report will be written meeting the standards specified in the CONSORT statement recommendations, and its extensions for non-inferiority trials. Baseline characteristics will be reported per group with descriptive statistics and no statistical tests. Statistical analysis will be performed with SAS V.9.4 and R V.3.3.1 (or the latest versions) software.

Primary outcome

A bilateral 95% CI of the difference in the caesarean rate between the experimental group (oxytocin) and the control group (prostaglandin) will be estimated. The upper bound of this CI will be compared with the non-inferiority margin (7%). A marker analysis with components of the Bishop score will be conducted.

Secondary outcomes

Time from inclusion to delivery in hours will be compared between groups using a Kaplan-Meier curve. For binary outcomes, the statistical analysis will be the same as for the primary outcome. The need for induction with oxytocin will be studied from descriptive statistics in the control group.

The outcomes related to satisfaction will be compared between the groups by χ^2 tests.

Health-economic outcome

Analyses will follow the French guidelines for economic evaluation in healthcare. Direct medical costs related to childbirth, possible antepartum stays ending in childbirth and the management of maternal and neonatal complications arising during the postpartum hospitalisation will be considered for the analysis. All the resources thus consumed by the women and their newborns will be retrospectively extracted from each centre's discharge database (Programme de Médicalisation du Système d'information). In the event of a transfer to another hospital after childbirth (eg, to bring the mother and child closer to home), the costs of this stay will be considered, if possible. The tariffs in force the last year of the study will be used to value the resources consumed from the perspective of the French health insurance system. The point estimate of the incremental cost-effectiveness ratio will be calculated as the difference in costs divided by the difference in caesarean delivery rates between the two strategies. The methodology proposed for combined clinical and economic non-inferiority studies will then be applied.[10] After bootstrapping, the proportion of incremental cost-effect pairs that lie in the non-inferiority area will be calculated for different values of the range of economic non-inferiority margins (≥0) and for a constant clinical non-inferiority margin (7%). A proportion will therefore be interpreted as the probability that induction of labour with oxytocin is clinically and economically non-inferior to the second cervical ripening for the given margins. A non-inferiority curve will be presented to show the uncertainty surrounding the economic non-inferiority margin.

Ethics

The sponsor and the investigator undertake to conduct the study in compliance with the French laws in force (Code de Santé Publique), the recommendations of French and international Good Clinical Practices (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use), the Declaration of Helsinki (Ethical Principles for Medical Research involving Human Subjects), and the European regulations related to clinical research.

The study will be conducted in accordance with this protocol. With the exclusion of emergency situations requiring specific therapeutic actions, the investigators guarantee that they will follow the protocol in all respects, in particular with regard to obtaining consent and reporting and monitoring serious adverse events.

This research is registered in the European EudraCT database under no 2021-000989-15 registration number in accordance with art. L1121.15 of the French Public Health Act and at ClinicalTrial.gov as NCT04949633.

Patient and public involvement

Patients and public were not involved in the design of this trial.

Dissemination

The coordinating investigator must approve in advance any written or oral communication of the study's results. Publication of the results will mention the sponsor and the funding source and will be written following the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals

(updated in December 2014)[11] from the International Committee of Medical Journal Editors. Investigators not listed as authors will be listed as non-author contributors.

DISCUSSION

OPIC is the first trial to compare induction of labour by oxytocin to repeating cervical ripening among women with an unfavourable cervix after a first cervical ripening of 24 hours.

The main bias of this trial is the absence of blinding. This flaw is nonetheless standard in studies of labour induction and is due to the specific nature of this intervention. The strength of this trial is that it integrates with the obstetric outcomes both maternal satisfaction outcomes and as economic considerations, neither previously included in this context. Because a negative birth experience has been linked to postpartum depression and post-traumatic stress syndrome,[12 13] fear of subsequent birth, desire for a future elective caesarean[14] and in some cases an increased likelihood of not wanting more children,[15] maternal satisfaction is a key issue in obstetric care. In the event that the two strategies show equivalent efficacy in obtaining vaginal deliveries in this situation where women have an unfavourable cervix after cervical ripening, the strategy to be privileged should be that associated with the best maternal satisfaction, given its priority in obstetric care today.

We hypothesised that a second cervical ripening might be an unnecessary procedure that instead lengthens the time to delivery and decreases maternal satisfaction with childbirth in comparison to oxytocin. Proving this would provide evidence to support our hypothesis that cervical ripening should not be repeated and that women with a Bishop score ≤6 after their first ripening procedure should be transferred to the labour ward for induction of labour with oxytocin, regardless of their cervical status. This would make it possible to avoid unnecessary exposure of patients to cervical ripening agents and to reduce both time to delivery and length of stay. The time spent on the ward is not only associated with maternal satisfaction but is also an important issue from an organisational point of view, as some centres have too few labour beds, and from an economic perspective, as increased length of stay increases the cost of care.

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Contributors CD conceived the study. CD, ALG and FM developed the study protocol. CD, ALG, FM and MDB draft manuscript preparation. CD, MDB, ALG, FM, DG, LS, NW, GL, RD, AG, JP, BG, TB, FP and SB-H edited the manuscript and read and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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