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# Assessment of an intervention to optimise antenatal management of women admitted with preterm labour and intact membranes using amniocentesis-based predictive risk models: study protocol for a randomised controlled trial (OPTIM-PTL Study)

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## ABSTRACT

**Introduction** The majority of women admitted with threatened preterm labour (PTL) do not delivery prematurely. While those with microbial invasion of the amniotic cavity (MIAC) represent the highest risk group, this is a condition that is not routinely ruled out since it requires amniocentesis. Identification of low-risk or high-risk cases might allow individualisation of care, that is, reducing overtreatment with corticosteroids and shorten hospital stay in low-risk women, while allowing early antibiotic therapy in those with MIAC. Benefits versus risks of amniocentesis-based predictor models of spontaneous delivery within 7 days and/or MIAC have not been evaluated.

**Methods and analysis** This will be a Spanish randomised, multicentre clinical trial in singleton pregnancies (23.0–34.6 weeks) with PTL, conducted in 13 tertiary centres. The intervention arm will consist in the use of amniocentesis-based predictor models: if *low risk,* hospital discharge within 24 hours of results with no further medication will be recommended. If *high risk,* antibiotics will be added to standard management. The control group will be managed according to standard institutional protocols, without performing amniocentesis for this indication. The primary outcome will be total antenatal doses of corticosteroids, and secondary outcomes will be days of maternal stay and the occurrence of clinical chorioamnionitis. A cost analysis will be undertaken. To observe a reduction from 90% to 70% in corticosteroid doses, a reduction in 1 day of hospital stay (SD of 2) and a reduction from 24% to 12% of clinical chorioamnionitis, a total of 340 eligible patients randomised 1 to 1 to each study arm is required (power of 80%, with type I error $\alpha$=0.05 and two-sided test, considering a dropout rate of 20%). Randomisation will be stratified by gestational age and centre.

**Ethics and dissemination** Prior to receiving approval from the Ethics Committee (HCB/2020/1356) and the Spanish Agency of Medicines and Medical Devices (AEMPS) (identification number: 2020-005-202-26), the trial was registered in the European Union Drug Regulating Authorities Clinical Trials database (2020-005202-26). AEMPS approved the trial as a low-intervention trial. All participants will be required to provide written informed consent. Findings will be disseminated through workshops, peer-reviewed publications and national/international conferences.

**Protocol version** V.4 10 May 2021.

**Trial registration numbers** NCT04831086 and Eudract number 2020-005202-26.

## Strengths and limitations of this study

- This is the first randomised clinical trial to evaluate whether amniocentesis-based predictive risk models allow optimising antenatal management of preterm labour.
- The study is adequately powered to test the main hypotheses regarding doses of antenatal corticosteroids, maternal length of hospital stay and the occurrence of clinical chorioamnionitis.
- However, we acknowledge that the sample size lacks statistical power to show differences in serious neonatal outcomes.

## INTRODUCTION

Spontaneous preterm delivery (sPTD) is the most common complication in human pregnancy, affecting 6.5%–9% of all deliveries.[1] sPTD is the first cause of neonatal morbidity and mortality and the second cause in children under 5 years of age, with the prevalence being

inversely proportional to gestational age at delivery. sPTD is preceded by threatened preterm labour (PTL) defined as the presence of uterine contractions and shortening of the uterine cervix. Women with PTL are routinely managed with hospital admission, tocolytic medications and corticosteroids to promote fetal lung maturation. However, current routine management strategies fail to distinguish low-risk from high-risk women with sPTD, leading to problems of overtreatment and undertreatment.

On one hand, low-risk women are unnecessarily treated. Indeed, only around 10% of pregnant women with clinical PTL deliver within the following 7 days, and 70% will deliver above 37.0 weeks of gestation.[1] While the rates are slightly higher in PTL presenting at or before 34 weeks of gestation, a substantial proportion of women admitted for PTL is still treated with several doses of antenatal corticosteroids, which promote lung maturation.[2] However, the trade-off of this treatment is deleterious neurodevelopmental effects, even in neonates finally delivered near term, and long-term cardiovascular and metabolic effects in infants and adults.[3 4]

On the other hand, a proportion of women with PTL at true high risk due to the presence of infection may not be treated timely. One of the aetiologies involved in sPTD is microbial invasion of the amniotic cavity (MIAC), which is often accompanied by intra-amniotic inflammation (IAI).[5–7] Up to 40% of pregnant women diagnosed with PTL before 32 weeks can have MIAC and/or IAI,[5] and these women have a shorter latency from the onset of symptoms to delivery (median 2 vs 50 days) and an earlier gestational age at delivery (median 27 vs 35 weeks of gestation) compared with those without MIAC and/or IAI.[8] Recent evidence suggests that early antibiotic therapy may reduce perinatal outcomes in PTL with MIAC.[9] However, antibiotics are not routinely used in PTL unless clinical chorioamnionitis is diagnosed.

We have developed predictive risk models of sPTD within 7 days and of MIAC in women with PTL,[8] which include gestational age at admission, cervical length by ultrasound, maternal blood C reactive protein (CRP) and amniotic fluid glucose and interleukin (IL) 6 concentrations. In previous studies, we have reported that these models allow a rapid result (hours) to predict whether a women admitted with PTL has a low or high risk of delivery within 7 days or MIAC.[8 10] However, these models require the use of amniocentesis, and their potential impact in clinical practice and the benefit-risk balance have not been evaluated in controlled clinical trials.

The main objective of this trial will be to evaluate the hypothesis that the clinical use of amniocentesis-based predictive risk models in women admitted with PTL reduces the use of antenatal corticosteroids and length of hospital stay due to optimised clinical management in women classified as low risk while reducing the occurrence of clinical chorioamnionitis due to early antibiotic treatment in those classified as high risk. As secondary aims, we will evaluate if the use of amniocentesis-based predictive risk models in PTL is cost-effective.

## METHODS AND ANALYSIS

### Study population

Pregnant women with singleton gestations between 23.0 and 34.6 weeks admitted with a diagnosis of PTL with intact amniotic membranes. PTL will be defined as the presence of uterine contractions with a frequency of at least two every 10 min and cervical changes (transvaginal ultrasound cervical length <25 mm).

### Type of study

Spanish randomised, multicentre clinical trial conducted in 13 tertiary centres. The trial will have two study arms: the intervention arm (individualisation of standard management based on amniocentesis-based predictive risk models) and the control arm (following the usual clinical protocols of each centre).

### Centres

Hospital Clínic, Hospital La Paz, Hospital Puerta del Mar, Hospital Virgen del Rocío, Hospital Germans Trias I Pujol, Hospital La Fe, Hospital Sant Joan de Déu, Hospital Vall d'Hebrón, Hospital 12 Octubre, Hospital Universitari Parc Taulí, Hospital de la Santa Creu I de Sant Pau, Hospital Clínico Universitario de Zaragoza and Consorci de Terrassa.

### Definitions of outcomes

1. Main outcome
   - Antenatal corticosteroid doses administered.
2. Secondary outcomes
   - Maternal length of hospital stay (days).
   - Occurrence of clinical chorioamnionitis (yes/no).
3. Other outcomes
   - Tocolysis duration (days) and antibiotic treatment (yes/no).
   - Gestational age at delivery (weeks).
   - Spontaneous delivery within 7 days after admission (yes/no), defined as a latency from admission to delivery less than or equal to 7 days. Women who deliver because of maternal or fetal indications will be consequently censored. Gestational age will be established according to crown-rump length at the first-trimester ultrasound scan.
   - MIAC (yes/no), defined as the presence of microorganisms in the amniotic fluid identified using aerobic/anaerobic/genital mycoplasma cultures or 16S ribosomal RNA (rRNA) gene sequencing.
   - Cost analyses: costs will be calculated as the product of resource use and unit costs. Resource use during the study period will be documented. The following resource items will be collected: maternal and neonatal admissions, method of delivery, type of induction, outpatient visits, emergency visits, medication, surgical procedures and maternal length of hospital stay. Maternal admissions will be differentiated into three levels of care: intensive, medium and ward. Neonatal admissions will be divided into four levels of care: intensive, high, medium and ward. Ward admissions of

newborns have not been calculated; these costs have already been incorporated in costs of maternal ward admissions.
- Maternal morbidity (yes/no) including intrapartum fever, endometritis, infection of surgical wound, sepsis, curettage, admission to intensive care unit, hysterectomy, need for transfusion and maternal death.
- A composite adverse neonatal outcome (yes/no) is defined as the presence of one or more of the following outcomes: fetal or neonatal death, early-onset sepsis, moderate/severe bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, surgical necrotising enterocolitis and retinopathy requiring laser treatment.
- Neonatal length of hospital stay (days).
- Neonatal anthropometric measurements: birth weight; height; cephalic, thoracic and abdominal perimeters; and arm circumference.

### Formula of the amniocentesis-based predictive risk models

Multivariable analysis by forward stepwise logistic regression was used to construct the amniocentesis-based predictive risk models of spontaneous delivery within 7 days and of MIAC (derivation cohort 263 women). Godness-of-fit models were assessed by calculating Nagelkerke's R2 (5).

The regression formula for spontaneous delivery within 7 days was −7.588+0.132 * gestational age at admission (weeks) − 0.051 * ultrasound cervical length (mm) − 0.055 * amniotic fluid glucose (mg/dL) + 1.438 * amniotic fluid $\log_{10}$ (IL-6). R2=51.5%.

The regression formula for MIAC was 1.034+0.169 * maternal CRP (mg/L) − 0.158 * amniotic fluid glucose (mg/dL). R2=65.6%.[5]

The diagnostic performance of these amniocentesis-based predictive risk models was calculated in a validation group of 95 women with PTL.[5]

### Selection of participants

Pregnant women with singleton gestations admitted with a diagnosis of PTL between 23.0 and 34.6 weeks will be eligible.

### Inclusion criteria

Singleton pregnancies admitted with a diagnosis of PTL between 23.0 and 34.6 weeks, not in arrested labour at randomisation, and who do not meet exclusion criteria.

### Exclusion criteria

Maternal age <18 years, multiple gestations, clinical chorioamnionitis at randomisation (defined by the presence of fever ≥38°C, fetal tachycardia (>160 heart beat per minute >10 min) and maternal white blood cells >15 000/$mm^3$ (not justified by the administration of antenatal corticosteroids), cervical dilatation >3 cm and major structural malformations of fetal complications that affect neurodevelopmental outcomes and not feasible to perform amniocentesis (amniocentesis-based predictive risk models include information of amniotic fluid: glucose and IL-6 concentrations).

### Intervention

The initial management of women with PTL will follow the standard institutional management of each centre and include the first dose of corticosteroids and tocolysis. Magnesium sulfate will be administered only with suspicion of imminent delivery. After obtaining written informed consent from each woman (online supplemental file 1), the patients will be randomly assigned to one of the two study arms in a 1:1 ratio. Randomisation will be stratified by gestational age (24.0–27.6, 28.0–31.6 and >32.0 weeks of gestation) and centre. The randomisation sequence will be computer-generated and will be implemented using a centralised controlled website randomisation service and electronic data capture system (REDCap V.10.8.2). Neither the investigators nor the trial coordinator will have access to the randomisation sequence:

1. In the *intervention arm*, the management will be optimised according to amniocentesis-based predictive risk models. High risk of sPTD within 7 days will be defined when the risk is >10%. We decided to select a cut-off with a high detection rate because our management (regarding doses of corticosteroids or maternal hospital stay) will be minimised if the predicted risk is low. High risk of MIAC will be defined when the risk is >20%. We decided to select a cut-off with a low false-positive rate to avoid unnecessary antibiotic administration:
   - In women classified as *low-risk women for sPTD within 7 days or MIAC*, hospital discharge within 24 hours of results with no further medication will be recommended.
   - In women classified as *high risk of sPTD within 7 days or MIAC*, antibiotics will be added to the standard management:
     - If *high risk of MIAC*, with broad-spectrum antibiotics (ampicillin 2 g/6 hours endovenous (ev) + ceftriaxone 1 g/12 hours ev + clarithromycin 500 mg/12 hours oral (vo)). In penicillin allergies: teicoplanin 600 mg/24 hours ev + aztreonam 1 g/8 hours ev + clarithromycin 500 mg/12 hours vo). On confirmation of MIAC and if women have not delivered, treatment will be adjusted according to the virulence of the microorganisms isolated. If the microbiological results are negative, antibiotic treatment will be discontinued.
     - If there is *high risk of delivery within 7 days but low risk of MIAC*, the women will be treated with only clarithromycin 500 mg/12 hours vo during 5–7 days. Clarithromycin will be used due to its demonstrated efficacy as anti-inflammatory treatment, since the amniocentesis-based predictive risk model of delivery within 7 days includes the inflammatory marker IL-6.
2. Women in the *control group* will be managed according to the standard institutional management protocols of each centre, including hospital admission, corticosteroids and tocolysis, without performing amniocentesis for this indication. Despite allocation in the control

group, amniocentesis will be performed in cases with suspicion of clinical chorioamnionitis.

The same study variables will be collected in both arms. We will collect the baseline characteristics and gestational age at delivery of women who were eligible but were finally not included in the trial.

### Duration of the study

We plan a study duration of 3 years.

### Sample size calculation

The sample size has been calculated to reduce antenatal corticosteroids doses, maternal length of hospital stay and the occurrence of clinical chorioamnionitis in the intervention arm.

The prevalence of women at low risk (of delivery within 7 days or presenting MIAC) is around 60%. The rate of pregnant women diagnosed with PTL who receive at least one course (two doses) of antenatal corticosteroids is around 90%. The rate of clinical chorioamnionitis in women with PTL below 34 weeks is 24% (project leader data).

In order to observe a reduction of a course of antenatal corticosteroids from 90% to 70% in the intervention arm, we would need 66 pregnant women per arm. Since the prevalence of this low-risk group might vary according to the centre, we plan to include 102–156 women to achieve significant differences.

In addition, we have also calculated the sample size needed to reduce the length of maternal hospital stay. The mean hospital stay in the project leader's centre is 3.5 days (SD 1.3–2). To reduce the hospital stay to 1 day (SD 2), in the intervention arm, we would need 70 women per arm. Since this length of stay might change according to the centre, we estimated the inclusion of 108–156 women per arm to achieve significant differences.

To reduce the occurrence of clinical chorioamnionitis in women with PTL below 34 weeks from 24% to 12%, we need 126 women per arm.

Therefore, taking into consideration 20% of dropouts, we estimate that a sample size of around 170 pregnant women per arm will be sufficient to detect with an error I of 5% and a power of 80%. As a limitation, we acknowledge that the sample size lacks statistical power to show differences in serious neonatal outcomes, that is, sepsis, due to the low prevalence of these neonatal outcomes. Despite this limitation, we expect to find a tendency in the results.

### Statistical analysis

A specific database using the Research Electronic Data Capture (REDCap) management platform (REDCap V. 10.8.2) will be created for the management and processing of the information obtained, in which the participant's data will be encoded. As a general rule, qualitative variables will be described as absolute frequencies and relative percentages and quantitative variables as means and medians for the assessment of central tendency and SD and IQR for the assessment of dispersion. In the case of ordinal variables, the description of both forms will be evaluated. Univariate analysis: for the comparison of two qualitative variables, the $\chi^2$ test or Fisher's exact test will be used. When the variables are quantitative, Student's t-test for independent samples or the Mann-Whitney U test will be used if the applicability criteria are not met. Multivariate analysis will be performed by means of multiple (continuous variables) or logistic linear regression (categorical variables) controlling the possible confounding factors. For statistical analysis, values of $p \leq 0.05$ will be considered as statistically significant. The data will be analysed with the SPSS programme (V.20.0, IMB or newer) and Stata for Mac (V.15.1 or newer).

### Data analysis plan

1. Creation of electronic data capture using the REDCap platform including online randomisation (stratified by centre and by gestational age at randomisation): January 2021 to March 2021.
2. Study initiation: May 2021.
3. Recruitment and follow-up including the inclusion of eligible women, randomisation process, antenatal management according to the study arm and follow-up until delivery and coding data: May 2021 to April 2023.
4. Monitoring visits to audit the trial by a Clinical Research Organization (CRO). It is planned to monitor each centre once a year including the study initiation visit and the study closeout visit (total number of four visits per centre): May 2021 to June 2023.
5. Adverse events and other unintended effects of trial interventions will be reported to Spanish Agency of Medicines and Medical Devices (AEMPS) and CRO immediately or within 48 hours.
6. Interim analysis plan: An interim analysis plan of results will be performed by an independent Data and Safety Monitoring Board (DSMB) midterm during the trial: April 2022. This group will be formed by clinicians and biostatisticians appointed by but independent from the study sponsors. The DSMB will provide assessment of the safety, scientific validity and integrity of the trial and will make the final decision to continue or terminate the trial.
7. Last patient included and randomised: April 2023.
8. Study closeout: June 2023.
9. Final statistical analysis: September 2023.
10. Preparation of manuscript for publication in a high-impact journal: December 2023 to February 2024.

### Patient and public involvement

Patients and the public will not be involved in the study design or conduct of the study or in any plans to disseminate the results to study participants.

### Ethics and dissemination

Prior to receiving approval from the Ethics Committee (HCB/2020/1356) and the AEMPS (identification number: 2020-005-202-26), the trial was registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (2020-005202-26). AEMPS

approved the trial as a low-intervention trial. All participants will be required to provide written informed consent. Any protocol modification change will be properly communicated to all relevant parties (investigators, Ethics Committee, AEMPS and EudraCT authorities).

The study has been registered in reec.aemps.es and ClinicalTrials.org.

The project results will be disseminated in international scientific congresses in the fields of fetal medicine (eg, International Society of Ultrasound in Obstetrics and Gynecology, Fetal Medicine World Congress and Society for Maternal-Fetal Medicine), as well in the form of extended abstracts, international conference proceedings and research articles in high-rank indexed journals.

## DISCUSSION

To our knowledge, this is the first randomised clinical trial to evaluate whether amniocentesis-based predictive risk models allow optimising antenatal management of women with PTL without affecting perinatal outcomes.

This prospective, randomised, multicentre, controlled trial is adequately powered to test the main hypotheses regarding doses of antenatal corticosteroids, maternal length of hospital stay and the occurrence of clinical chorioamnionitis.

The treatments used in the clinical management in this trial are already commercialised; there is international consensus about their use in the management of PTL, with an enormous literature base supporting their use for the indications proposed in the trial.

Since a potential limitation is slow recruitment due to the decline in birth rates, the trial has been designed as a multicentre trial. Moreover, we acknowledge that the sample size lacks statistical power to show differences in serious neonatal outcomes, that is, sepsis, due to the low prevalence of these outcomes. Despite this limitation, we expect to find a tendency in our results.

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**Correction notice** This article has been corrected since it was published. The spelling of collaborator 'Cecilia Vilalain González' has been corrected.

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**Contributors** TC, MP and EG conceived and will supervise the project. TC, MP, VA and FF designed the experiment. TC, MP, JLB, FB, VD-A, MG, IH, AO, AV, SF, MPC-B, CC, LM-M and CP will participate in the inclusion of women, obtainment of consent form signatures, randomisation, data coding and management of women until delivery. TC, MP, FF, VA and EG will analyse and interpret the data. TC, MP, JLB, FB, VD-A, MG, IH, AO, AV, SF, FF, MPC-B, CC, LM-M, CP and EG will cowrite and revise the manuscript. MP and EG equally contributed as last authors.

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