

## PRETERM PRELABOUR RUPTURE OF MEMBRANES AT TERM AND PRETERM

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### 1. DEFINITION

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The Preterm Prelabour Rupture Of Membranes (PPROM) is the rupture of the ovular membranes before the start of the labour, with the consequent leakage of amniotic fluid. Most PPROMs are at term (8% of gestations) and labour will be spontaneously triggered, even in unfavourable cervical conditions, in the following 24 hours (72%-95%). What is more infrequent is the preterm PPROM, which complicates 2-4% of all singleton pregnancies, 7-20% of multiple pregnancies, and represents 30% of preterm labours<sup>1</sup>. Due to the fact that the viability limit has been reduced in recent years, today we refer to previable PPROM when it occurs before week 23.0 of gestation.

### 2. DIAGNOSIS

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The PPROM diagnosis is clinical, showing hydrorrhea in the vaginal examination. In case of clinical doubt, perform the following:

2.1 Vaginal pH (normal pH 3.4-5.5): this is a colorimetric test. The amniotic fluid is alkaline (pH > to 6.5). It presents false positives (semen, urine, blood, bacterial vaginosis) and false negatives (candidiasis).

2.2 Fetal sonogram: evidence of oligohydramnios not previously existing. It has a low sensitivity and specificity.

Neither test being very specific and conclusive, for cases in which diagnostic doubt persists, perform the following:

2.3 Biochemical tests:

2.3.1 Insulin-like Growth Factor Binding Protein-1 (IGFBP-1): its sensitivity varies from 74-100% and its specificity from 77-98.2%.

3.2.1 Placental Alpha Microglobulin-1 (**PAMG-1**): its sensitivity is close to 99% and specificity varies from 87.5-100%.

Both tests have similar sensitivity and specificity, so they can be used interchangeably in cases where there is a diagnostic doubt about the rupture of membranes<sup>2</sup>.

2.4 Diagnostic amniocentesis. In very select cases, the definitive diagnosis can be made by **instilling**

**fluorescein** (1 mL of fluorescein diluted in 9 mL of physiologic serum) into the amniotic cavity by means of amniocentesis. The detection of fluorescein in a vaginal gauze after 30-60 minutes confirms the diagnosis of PPRM, although after this time it loses specificity.

In **advanced dilatations** with exposed membranes, both biochemical tests and amniocentesis with fluorescein instillation can show **false positives**.

### 3. PREGNANCIES AT TERM

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In pregnant women with PPRM at term, immediate delivery of pregnancy (upon admission) or in the subsequent 24 hours is associated with a lower risk of clinical chorioamnionitis and endometritis than expectant management, without increasing the risk of maternal or neonatal morbimortality, or the rate of caesarean sections or operative vaginal deliveries, or the risk of neonatal sepsis<sup>3</sup>. Both induction methods (maturation with prostaglandins or induction with oxytocin) have similar perinatal results, although it has been observed that induction with oxytocin is associated with a shorter latency to delivery and with a lower risk of chorioamnionitis<sup>4</sup>. Finally, in PPRM at term, unlike those at preterm, there is no universal consensus regarding the use of antibiotics.

Knowing this, our management of PPRM at term will differ based on the PPRM evolution hours:

#### **PREGNANT WOMAN WITH PRELABOUR RUPTURE OF MEMBRANES OF LESS THAN 24 HOURS OF EVOLUTION:**

3.1 Complementary tests: upon admission, a haemogram or C-reactive protein (CRP) will NOT be necessary.

3.2 Antibiotherapy: there is insufficient evidence to justify antibiotic prophylaxis in PPRM at term, except in cases of carriers of *Streptococcus agalactiae*. This is why, if PPRM < 24h and negative *S. agalactiae*, we will NOT start antibiotherapy at induction. Only in **positive S. agalactiae** patients, will we administer antibiotic upon admission as follows:

3.2.1 **If uterine contractions**: endovenous (ev) penicillin 5 M + penicillin 2.5 M/4 h ev or ampicillin 2g ev +1 g/4 h ev.

3.2.2 **If NO uterine contractions**: amoxicillin/clavulanic acid 1 g/6 h ev (it has greater coverage against microorganisms than penicillin).

3.2.3 **Allergies**: clindamycin 900 mg/8 h ev (only if the antibiogram is sensitive). If it is resistant to clindamycin or antibiogram is unknown, teicoplanin 600 mg/24 h ev.

3.3 Indication for delivery: although expectant management will be respected in those women who request it, **our recommendation** in a woman with PPRM who has not started labour will be to **actively induce**

**delivery** in the hours following admission. The induction method will depend on the cervical conditions, although aspects such as the pregnant woman's nightly rest and the preferences will be valued.

#### **PREGNANT WOMAN WITH PPROM OF 24 HOURS OF EVOLUTION OR MORE:**

3.4 Complementary tests: upon admission, a haemogram and a CRP will be requested.

3.5 Antibiotherapy: start upon admission **amoxicillin/clavulanic 1 g/6 hours ev**, regardless of *S. agalactiae* carrier status. **Allergies**: the treatment of choice is clindamycin 900 mg/8 h ev (if sensitive antibiogram) or teicoplanin 600 mg/24 h ev (if resistant to clindamycin or unknown antibiogram).

3.6 Indication for delivery: the delivery will be planned upon admission. The induction method will depend on the cervical conditions, although aspects such as the pregnant woman's nightly rest, parity and the patient's preferences will be valued.

#### **4. PRETERM PPROM**

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##### **GENERAL CONSIDERATIONS** when handling **EMERGENCIES**:

4.1 **Determination of gestational age**. If possible, using the first trimester ultrasound.

4.2 Rule out the presence of other risk factors through medical history and examination.

4.3 **Avoid multiple vaginal examinations** in these pregnant women, except for regular uterine contractions that require assessment of obstetric conditions. The cervical assessment will be performed using:

- a. Vaginal speculum
- b. Cervical length ultrasound

4.4 Complementary tests

4.4.1. **Haemogram, CRP, coagulation tests** (the latter if not updated in the last 2 months).

4.4.2. **Non-Stress Test (NST)** (EMERGENCIES): to assess fetal wellbeing and rule out the presence of uterine contractions and/or signs suggesting infection (fetal tachycardia).

4.4.3. **Basic fetal ultrasound: fetal presentation, fetal growth, amniotic fluid.**

4.5. Antibiotherapy: **broad spectrum antibiotic prophylaxis** will be started with **ampicillin 2 g/6 h ev + ceftriaxone 1 g/12 h ev + oral clarithromycin 500 mg/12 h**. The proposed antibiotic prophylaxis is broad-spectrum, has good safety (regarding toxicity) for both the foetus and the mother, and penetrates completely, within a few hours, into tissues such as the placenta.

### Considerations with antibiotherapy:

- 4.5.1 In case of **allergies to penicillin or beta-lactams ( $\beta$ -lactams)**: the prophylaxis of choice will be the combination of **teicoplanin 600 mg/24 h ev + aztreonam 1 g/8 h ev + oral clarithromycin 500 mg/12 h**. Their use as prophylaxis for PPRM does not increase the risk of resistance, so they will continue to be drugs of choice when used to treat infections caused by germs sensitive to them.
- 4.5.2 As an exception to the proposed prophylaxis, in pregnant women **with a positive urine culture** (regardless of the gestation trimester) for ESBLs (extended-spectrum  $\beta$ -lactamase)-producing Gram-negative bacteria, ceftriaxone will be replaced by antibiotherapy sensitive to Gram-negative ESBLs according to antibiogram. In the case of not having an antibiogram, **ertapenem 1 g/24 h ev** will be administered. The rest of the antibiotics (ampicillin 2 g/6 h ev + oral clarithromycin 500 mg/12 h) will remain unchanged.
- 4.5.3 Finally, it must be considered that there are some women with a higher risk of being carriers of ESBL- or  $\beta$ -lactamase-producing Gram-negative bacteria
- a. Previous infection or colonisation in the last 6 months by ESBL (or other methicillin resistant *Staphylococcus aureus*) ( $\beta$ -lactamase- or extended-spectrum  $\beta$ -lactamase- producing Gram-negative bacteria) (major criterion)
  - b. Or 2 or more of the following factors:
    - i. Comorbidity (chronic kidney disease), pregestational diabetes mellitus, heart disease, chronic obstructive pulmonary disease, immunosuppression (neutropenic patients), solid organ transplant or hematopoietic stem-cell transplant, corticosteroids (>20 mg/day of prednisone or equivalent for more than 2 weeks), immunosuppressants or cytostatics, HIV (human immunodeficiency virus) with less than 200 CD4+, primary immunodeficiencies).
    - ii. Vesicle catheter wearer.
    - iii. History of **hospital admission for more than 72 hours** in the previous 3 months.
    - iv. Use of **systemic (oral or intravenous) antibiotics for 5 days or more** in the previous 3 months (frequent in patients with recurrent urinary tract infections).
    - v. Coming from endemic areas (Latin America, Caribbean, Asia, non-EU Mediterranean Region) who have lived in our country for less than 6 months.

When there are these risk factors (1 major or 2 minor), or if there is growth of ESBL germs, ampicillin 2 g/6 h iv + **ertapenem 1 g/24 h iv** + oral clarithromycin 250 mg/12 h will be administered. In these selected cases, an **anal pap smear** will be taken for ESBL screening upon admission, since, if delivery occurs or clinical chorioamnionitis develops, it may be important information for the obstetrician and neonatologist. **If the anal smear rules out the presence of multidrug resistant Gram-negative bacilli, ertapenem will be replaced by ceftriaxone 1 g/12 h ev while antibiotic prophylaxis lasts.**

4.6 indication for delivery: in the event of **clinical chorioamnionitis or non-reassuring fetal status**, delivery will be indicated **regardless of gestational age**.

In the absence of these complications, the clinical management of these women will be individualised based on gestational age, estimating the risk for the mother, for the foetus, and neonatal complication derived from preterm labour.

#### **GESTATIONS OF 35.0 – 36.6 WEEKS**

4.7 Hospital admission.

4.8 Antibiotherapy: upon admission, broad-spectrum prophylactic antibiotherapy will be started with **ampicillin 2 g/6 h iv + ceftriaxone 1 g/12 h iv + oral clarithromycin 500 mg/12 h**. Apply the same considerations regarding antibiotherapy as in the previous section regarding allergies and ESBL germs.

4.9 Corticotherapy: **NOT** indicated.

4.10 Tocolysis: **NOT** indicated.

4.11 Indication for delivery: same management as for PPROM at term.

#### **GESTATIONS OF 23.0 – 34.6 WEEKS**

4.12 Hospital admission.

4.13 Supplementary tests. In addition to haemogram, CRP, NST, Emergency fetal ultrasound:

4.13.1 **Urine culture** (to rule out asymptomatic bacteriuria).

4.13.2 **Vagino-rectal sampling for screening of Streptococcus agalactiae** if it has not been performed in the previous five weeks.

4.13.3 **Endocervical cultures will be performed only** if the patient presents symptoms of **vaginitis** (e.g. pruritus with white lumpy leukorrhea), suspected **bacterial vaginosis** or if PPROM occurs in pregnant women with **cervical cerclage**.

**Diagnostic amniocentesis**<sup>5</sup>. The main maternal complication of PPROM is the infectious complication (**38% of women with PPROM below 34.0 weeks**)<sup>6</sup>, representing the most frequent known aetiology associated with PPROM in these women. In our centre, **amniocentesis** will be proposed to rule out subclinical intra-amniotic infection in PPROM that starts between **20.0-34.0 weeks of gestation**, trying targeted treatment if possible, based on variables such as gestational age, type of isolated germ, and if the maternal and fetal status allow it. This strategy also aims to avoid unnecessary prolongation of the antibiotic treatment, reducing the potential risk of anaphylaxis, the emergence of resistance and the selection of the most pathogenic microorganisms.

Amniocentesis will preferably be performed before the administration of corticoids and of antibiotics, so as not to mask the results of the cultures, but it will be done **regardless of the time-lapse from amniorrhexis to admission or the start of antibiotic treatment.**

The risks of the test are minimal (< 0.5%)<sup>7</sup>. It will be performed, with prior informed consent and evaluating the maternal serologic status (annex 1), with a 22G (o 20G) needle. 20cc will be drawn to determine:

- Glucose in amniotic fluid,
- Gram stain in amniotic fluid,
- Culture of aerobic and anaerobic amniotic fluid, and
- Culture of amniotic fluid for genital mycoplasma.
- In some very selected cases in which there is a discrepancy between the results of glucose and Gram stain, the determination by CRP to detect the 16S rRNAs will be carried out. 16S is a fragment of the ribosomal RNA present in bacteria, so if it is detected by CRP techniques, it suggests the presence of intra-amniotic infection.

In **singleton pregnancies > 34.0 weeks** or **multiple pregnancies**, **amniocentesis will not be systematically proposed**, since the prevalence of intra-amniotic infection in these cases is low, although it **should be assessed if there is a clinical suspicion** of infection (e.g. increasing CRP, low-grade fever).

4.14.1 **Haemogram and CRP.** This will be performed on admission and daily for the first 3 days. It will subsequently be performed weekly unless there are clinical changes (e.g. low-grade fever or uterine dynamics) that make it necessary to rule out the presence of an infectious process. The haemogram and CRP will be some of the parameters to be assessed before deciding on medical discharge.

4.14.2 **Fetal wellbeing study** during hospitalisation if clinical stability:

- **NST:** if the NST is correct, it can be done every 24-48 hours.
- **Fetal ultrasound** once a week.

4.15. Antibiotherapy<sup>8</sup>: upon admission, broad-spectrum prophylactic antibiotherapy with **ampicilin 2 g/6 h iv + ceftriaxone 1 g/12 h iv + oral claritromycin 500 mg/12 h**. Apply the same considerations regarding allergy to penicillin and ESBL germs discussed in the previous sections.

4.16. Duration of antibiotherapy:

a) In the case of having performed a **diagnostic amniocentesis** upon admission:

- If glucose in amniotic fluid  $\geq$  14 mg/dL, Gram did not show germs and clinical and analytical stability: antibiotics will be suspended **48 hours after their start**.
- If glucose in amniotic fluid < 14 mg/dL, Gram did show germs or clinical and/or analytical alteration: antibiotics will be maintained **until the result of the amniotic fluid culture**, stopping them if the result is finally negative.
- Discrepancy in any of the results (glucose < 14 mg/dL with Gram/culture did not show

germs or Gram/culture did show germs but glucose  $\geq 14$  mg/dL): in these cases, the determination of **16S rRNA** in amniotic fluid will be requested. While awaiting the result, or in cases where it is not possible to determine, **we will continue the prophylactic antibiotherapy while awaiting the definitive culture. If the culture is negative, antibiotherapy will be stopped.**

- Culture of positive amniotic fluid: gestational age and germs are variables of enormous importance when considering delivery. If expectant management is chosen, treatment will be individualised based on the antibiogram and the treatment will be extended for **7-10 days**.

The treatment of choice in case of infections with *Ureaplasma* spp. is oral **clarithromycin 500 mg/8 h for 7-10 days** since it has enhanced bioavailability in placenta, amniotic fluid and foetus than azithromycin. As with azithromycin, an electrocardiogram will be performed in the initial days of diagnosis, since cases have been described, in polypathological patients, of Q-T interval increase after prolonged use.

In the event that Gram-negative bacilli, such as Klebsiella or Escherichia coli, are isolated, the microbiology department will test whether they are beta-lactamase-producing germs, with the aim of adjusting the antibiotic treatment and replacing the conventional regimen with **ampicillin 2 g/6 h + ertapenem 1 g/24 h iv + oral clarithromycin 250 mg/12 h**.

In any case, if the pregnancy prolongs, a new amniocentesis to assess whether it becomes negative after the antibiotic treatment might be considered.

- If **amniocentesis is not possible** (e.g.: anhydramnios), **prophylactic antibiotherapy** will be suspended after **48 h** as long as there are no analytical changes that generate suspicions about a presence of infection.
- If **symptoms suggestive of infection** (due to the onset of fever or increased CRP) **and taking prophylactic antibiotics** (ampicillin 2 t/6 h iv + ceftriaxone 1 g/12 h iv + oral clarithromycin 500 mg/12 h) **in the last 15 days**, if we do not have an antibiogram, we will **start treatment with piperacillin-tazobactam 4 g/6 h iv + oral clarithromycin 500 mg/12 h** until the culture results are available. Remember considerations in penicillin allergies and ESBL carriers.
- If **clinical chorioamnionitis** is suspected, the gestation delivery will be indicated under antibiotic coverage with **Piperacillin-tazobactam 4 g/6 h iv + oral clarithromycin 500 mg/12 h**. After delivery (regardless of whether vaginal delivery or caesarean section), the same antibiotic regimen will be maintained for up to 48 hours without fever. We will only maintain the post-partum antibiotic regimen in patients with persistent fever or with clinical, haemodynamic or analytical alterations that suggest a sepsis (or septic shock). In these cases, multidisciplinary management will be individualised.

4.17 Corticotherapy: intramuscular betamethasone 12 mg and repeat at 24 hours **between 23.0 and 34.6 weeks**. Fetal lung maturation might be considered between 22 and 23.0 weeks (following consensus with the parents and neonatology) if obstetric conditions suggest that delivery can occur around 23.0 weeks. In PPROM, there is controversy about the use of repeated doses of corticoids due to the increased risk of morbidity of infectious origin<sup>9, 10</sup>. Therefore, there is currently a tendency to be restrictive in the use of repeated doses of corticoids. Our recommendation will be to repeat booster doses only in the event of **destabilisation of the clinical case (e.g. onset of uterine contractions, vaginal bleeding, etc.) that suggests the imminence of the delivery or the need to deliver or if there is evidence of fetal lung immaturity**.

Remember that the administration of corticoids leads to maternal leukocytosis in the 5-7 days after its administration and a decrease in the variability in the NST without these factors necessarily translating into a septic condition or loss of fetal wellbeing.

4.18 Tocolysis: in the case of **PPROM, the use of tocolytics must be justified only with the objective of completing the fetal lung maturation and always in the absence of a diagnosis of chorioamnionitis or triple I**. At the onset of uterine contractions in women with PPROM, **intra-amniotic infection or clinical chorioamnionitis should be ruled out before introducing tocolysis** by means of laboratory tests (haemogram, CRP) and, if feasible, by amniocentesis.

4.19 General care during admission to the PPROM:

- Maternal rest allowing for personal hygiene and meals.
- Assess the need for prophylactic LMWH (low molecular weight heparin) according to criteria for a hospitalised patient.

4.20 Outpatient management:

In some selected cases of stable PPROM and based on **clinical variables** (clear hydorrhoea without uterine dynamics, patient compliance), **laboratory tests** (CRP, normal leukocytes upon discharge) and **sonograms** (maximum column of amniotic fluid > 2 cm, stable fetal presentation and cervical length) we could opt for outpatient management from the 3rd day of admission. In the rest of cases, the time of discharge will be individualised. Analytical and sonogram stability will be confirmed before the patient is approved for discharge. Outpatient control will be weekly: haemogram + CRP + Sonogram (cervical length, maximum column, amniotic fluid) in the preterm birth prevention clinic.

4.21 Indication for delivery:

There is currently controversy regarding the appropriate time of delivery in PPROM: expectant management from 34.0 weeks benefits the neonate (less respiratory morbidity, fewer admissions/days of admission in neonatal intensive care unit, higher birth weight) and mother (higher rate of spontaneous

onset of labour, fewer caesarean sections, greater maternal-fetal bond) although it increases the risk of intrapartum fever (2% vs. 1% in active induction) and haemorrhage before or during labour (5% vs. 3%, respectively)<sup>3</sup>.

That is why we will agree with the parents on the approach a) expectant management until 35.0 weeks (if PPRM  $\geq$  32.0 weeks) or b) delivery from 34.0 weeks once the lung maturation is completed (if PPRM < 32.0 weeks).

Advice from neonatology is recommended.

a) 48 h before planned delivery, lung maturity will be checked by applying:

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- If there is a low risk of neonatal respiratory morbidity, delivery will be planned without the need to repeat doses of corticoids.
- If there is a high risk of neonatal respiratory morbidity, administer booster dose of corticoids and plan delivery from 35.0 weeks.

b) At the time of labour, administer **intravenous penicillin** to reduce the risk of neonatal sepsis in **pregnant women with positive or unknown Streptococcus agalactiae in labour < 35 weeks/or if more than 5 weeks from the performance of the cultures**. In case of allergies: clindamycine 900 mg/8 h iv (only if the antibiogram is sensitive). If it is resistant to clindamycin or antibiogram is unknown, Teicoplanin 600 mg/24 h iv

c) If labour is expected to be imminent, consider **neuroprotection** with magnesium sulphate **until 32.0** weeks of gestation.

#### 4.22 Delivery indicated due to subclinical intra-amniotic infection

In the **confirmed cases of intra-amniotic infection** (Gram stain with visualisation of germs and/or positive amniotic fluid culture), the gestational age is vitally important and will determine our approach to management:

- If **< 23.0 weeks**, our recommendation will be delivery, given the poor fetal prognosis at these weeks of gestation and the maternal infectious risk.
- Between **23.0-26.0 weeks**, tocolysis will be allowed until fetal maturation is completed under antibiotic coverage, and always in the absence of a diagnosis of chorioamnionitis or Triple I. Depending on the germ, the gestational age and the maternal condition, management will be individualised after fetal maturation with the preterm birth prevention clinic.
- If **> 26.0 weeks**, antibiotic coverage and lung maturation will be initiated but tocolysis will not be administered. If labour does not occur spontaneously, management will be individualised according to the germ, gestational age and maternal condition, with the Preterm Birth Prevention Clinic.

## GESTATIONS OF <23.0 WEEKS

It is an infrequent obstetric complication (1-7/1000 gestations) but complex to manage that is associated with significant maternal morbidity and fetal morbimortality.

### 4.23 Hospital admission:

With respect to fetal viability, there is no consensus on the optimal obstetric management of these gestations, nor is there any reference in the literature on the risks and benefits of the outpatient vs. inpatient management approach until the moment of the delivery. As long as there is no clinical (or analytical) suspicion of chorioamnionitis or loss of fetal wellbeing or suspicion of fetal abruption **in gestations < 20.0 weeks, outpatient management and weekly monitoring with blood test control. Patients with PPROM at 20.0 weeks or thereafter, will be admitted.**

### 4.24 Complementary tests:

Same management as in PPROM at 24.0-35.0 weeks except in the case of diagnostic amniocentesis, which will be reserved for PPROM  $\geq$  20.0 weeks. Below this gestational age, it will only be performed if there is clinical suspicion of infection.

- a) In cases of recent **PPROM** after invasive **procedure**, consider **not** performing **amniocentesis** (low probability of intra-amniotic infection as a cause of the PPROM).
- b) In cases of a **positive culture of the amniotic fluid** before week 22.6, our recommendation is delivery, given the poor maternal and fetal prognosis due to the risk of infection and extreme prematurity.
- c) Consider including a **QF-PCR study in previable PPROM**.

4.25 Antibiotherapy: in the case of **PPROM < 20.0 weeks, outpatient** management under **amoxicillin-clavulanic acid 875 mg/ 8 h oral route** will be administered as a prophylactic antibiotic treatment **over the course of 48 h**. In case of hospital admission, the same management and intra-venous broad-spectrum antibiotic treatment proposed for the rest of the PPROM will be proposed.

4.26 Corticotherapy: if not given before, betamethasone 12 mg x 2 doses will be administered electively at 26-27 weeks. According to our own data, gestational age at delivery in these previable PPROM has a median of (25; 75 percentile) 26.9 (24.7-30.7) weeks, so prophylactically administering a course of corticoids at 26-27 weeks would ensure that antenatal lung maturation has been completed in most cases.

4.27 Hospital management: if the patient remains stable from the analytical and clinical point of view (see point 7, outpatient control PPROM 23-0-34.6 w) will be susceptible to outpatient management in the Preterm Birth Prevention Clinic. In the case that the patient with previable PPROM goes to Emergencies and there are clinical doubts (e.g. uterine dynamics, bleeding, increased hydorrhoea, etc.), hospital

admission will be assessed as well as lung maturation.

4.28 Prognosis of previable PPROM: the main contributors to the poor perinatal result in the case of previable PPROM depend mainly on the presence of severe (< 1 cm) and persistent (> 7 days) oligohydramnios:

- a) **Overall survival** described in our series is 40%<sup>11</sup>. If 24.0 weeks are reached, survival increases to 74%.
- b) **Neonatal morbidity** related to prematurity (dependent on gestational age)
- c) Risk of **clinical chorioamnionitis** due to prolonged rupture of membranes (33%)<sup>11</sup>.
- d) The risk of **global pulmonary hypoplasia** between 16-26 weeks varies from 1-27%<sup>11</sup>. In our series, it is 6%<sup>11</sup>. The risk increases if the oligohydramnios is early, severe (< 1 cm) and persistent.
- e) **Deformities or poor skeletal positions** (2-28%)<sup>11</sup>. In our series, 9%, and are usually reducible postnatally<sup>11</sup>.

If **maximum column of amniotic fluid < 2 cm a week** after admission, the fetal and maternal prognosis will be explained:

- The request to terminate the gestation is an option in Spain until week 22.6 given the poor fetal prognosis and the associated maternal-fetal morbidity (in relation to the risk of clinical chorioamnionitis, extreme prematurity and the risk of pulmonary hypoplasia).
- In those parents who opt for an expectant management, **outpatient management** in the Preterm Birth Prevention Clinic with weekly tests and ultrasound evaluation of the maximum column of amniotic fluid will be chosen. Depending on the findings, the management and eventual readmission and indication for delivery will be individualised. Advice from neonatology will also be considered in these cases.

4.29 Indication for delivery: delivery between 34.0 and 35.0 weeks will be individualised based on variables such as the evolution of the maximum column of amniotic fluid or the documented evidence of lung maturity. Our recommendation in case of subclinical intra-amniotic infection (by Gram stain or amniotic fluid culture) will be delivery at < 23.0 weeks of gestation.

## 5. CONDITIONS FOR PERFORMING AN AMNIOCENTESIS

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Prior to the procedure, it is necessary to know the RhD-red blood cells and serological status, HIV (human immunodeficiency virus), HBV (hepatitis B virus), HbsAg (hepatitis B surface antigen), which will be requested urgently if unknown. The HCV (hepatitis C virus) serologic assay will be requested only in high-risk pregnancies, where there is:

- History of parenteral drug use
- History of transfusion or transplant

- HIV or HBV or HCV infection
- Infected partner with HIV or HBV or HCV
- Chronic elevated transaminases
- Wearer of tattoos
- Piercings made with non-sterile or single-use material.

In general, it is preferable to **avoid a transplacental amniocentesis** as long as an extra-placental access is feasible. It should be avoided in gestations with positive serologies for HIV, HBV, and HCV.

In the case of maternal infection by HIV, HBV or HCV, the specific protocol for performing the invasive procedure is referred to, but the main peculiarities are summarised here:

- The risk-benefit ratio of diagnostic amniocentesis to evaluate intra-amniotic infection. It may be limited to cases with clinical suspicion of intra-amniotic infection. If it is considered indicated to perform it, transplacental passage should be avoided in the case of HIV, HBV or HCV infection.
- HIV positive: perform the procedure under **combined antiretroviral treatment** and, ideally, with an **undetectable viral load**. In the case of untreated HIV infection or detectable viral load, try to delay the procedure and reassess together with the Perinatal Infections Unit. If it is not possible to delay it, start the intravenous zidovudine protocol and assess the urgent start of **combined antiretroviral treatment**.
- HBV positive: in the case of positive hepatitis B-e antigen (HBe-Ag), positive viral load (DNA HBV), in unavoidable transplacental puncture or third-trimester amniocentesis, HBV-specific immunoglobulin will be administered after the procedure (600 IU intramuscular, single dose within 24 hours).
- HCV positive: the risk of vertical transmission of HCV through amniocentesis has been poorly evaluated. If possible, have HCV-RNA before the procedure.

## 6. BIBLIOGRAPHY

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1. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. *Am J Obstet Gynecol.* 2009;201(3):230-240.
2. Palacio M, Kuhnert M, Berger R, et al. Meta-analysis of studies on biochemical marker tests for the diagnosis of premature rupture of membranes: comparison of performance indexes. *BMC pregnancy and childbirth.* 2014;14:183.
3. Bond DM, Middleton P, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database Syst Rev.* 2017;3:CD004735.
4. Kulhan NG, Kulhan M. Labor induction in term nulliparous women with premature rupture of membranes: oxytocin versus dinoprostone. *Archives of medical science : AMS.* 2019;15(4):896-901.
5. Peng CC, Chang JH, Lin HY, et al. Intrauterine inflammation, infection, or both (Triple I): A new concept for chorioamnionitis. *Pediatrics and neonatology.* 2018;59(3):231-237.
6. Rodríguez-Trujillo A, Cobo T, Vives I, Bosch J, Kacerovsky M, Posadas DE, Angeles M, Gratacós E, Jacobsson B, Palacio M. Gestational age is more important for short-term neonatal outcome than microbial invasion of the amniotic cavity or intra-amniotic inflammation in preterm prelabor rupture of membranes. *Acta obstetrica et gynecologica Scandinavica.* 2016.
7. Stark CM, Smith RS, Lagrandeur RM, et al. Need for urgent delivery after third-trimester amniocentesis. *Obstetrics and gynecology.* 2000;95(1):48-50.
8. Johnson CT, Adami RR, Farzin A. Antibiotic Therapy for Chorioamnionitis to Reduce the Global Burden of Associated Disease. *Frontiers in pharmacology.* 2017;8:97.
9. Lee MJ, Davies J, Guinn D, et al. Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes. *Obstet Gynecol.* 2004;103(2):274-281.
10. Crowther CA, McKinlay CJ, Middleton P, et al. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database Syst Rev.* 2011(6):CD003935.
11. Munrós J CT, Ríos J, Ferreri J, Migliorelli F, Baños N, Rodríguez-Trujillo A, Gratacós E, Palacio M. Contribution of the amniotic fluid along gestation to the prediction of perinatal mortality in women with early preterm premature rupture of membranes. *PloS one.* 2016.
12. Johnson CT, Adami RR and Farzin A (2017) Antibiotic Therapy for Chorioamnionitis to Reduce the Global Burden of Associated Disease. *Front. Pharmacol.* 8:97.

**PRETERM PROM MANAGEMENT ALGORITHM**

**Antibiotherapy:** Ampicillin 2 g/6 h iv + ceftriaxone 1 g/12 h iv + oral claritromycin 500 mg/12 h x 48 h (or amoxicillin-oralclavulanic acid 875 mg/8 h x 48 h if no hospital admission and PPROM < 20 weeks). Special considerations if allergy to penicillin or ESBL-producing germ  
**Corticotherapy:** 23.0-34.6 weeks (12 mg betamethasone/ 24 h x 2 doses).

