Preterm premature rupture of the membranes: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF)

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Abstract

In France, the frequency of premature rupture of the membranes (PROM) is 2% to 3% before 37 weeks' gestation (level of evidence [LE] 2) and less than 1% before 34 weeks (LE2). Preterm delivery and intrauterine infection are the major complications of preterm PROM (PPROM) (LE2). Prolongation of the latency period is beneficial (LE2). Compared with other causes of preterm delivery, PPRM is associated with a clear excess risk of neonatal morbidity and mortality only in cases of intrauterine infection, which is linked to higher rates of in utero fetal death (LE3), early neonatal infection (LE2), and necrotizing enterocolitis (LE2).

The diagnosis of PPRM is principally clinical (professional consensus). Tests to detect IGFBP-1 or PAMG-1 are recommended in cases of uncertainty (professional consensus).

Hospitalization is recommended for women diagnosed with PPRM (professional consensus). Adequate evidence does not exist to support recommendations for or against initial tocolysis (Grade C). If tocolysis is prescribed, it should not continue longer than 48 hours (Grade C). The administration of antenatal corticosteroids is recommended for fetuses with a gestational age less than 34 weeks (Grade A) and magnesium sulfate if delivery is imminent before 32 weeks (Grade A). The prescription of antibiotic prophylaxis at admission is recommended (Grade A) to reduce neonatal and maternal morbidity (LE1). Amoxicillin, third-generation cephalosporins, and erythromycin (professional consensus) can each be used individually or erythromycin and amoxicillin can be combined (professional consensus) for a period of 7 days (Grade C). Nonetheless, it is acceptable to stop antibiotic prophylaxis when the initial vaginal sample is negative (professional consensus). The following are not recommended for antibiotic prophylaxis: amoxicillin-clavulanic acid (professional consensus), aminoglycosides, glycopeptides, first- or second-generation cephalosporins, clindamycin, or metronidazole (professional consensus).

Women who are clinically stable after at least 48 hours of hospital monitoring can be managed at home (professional consensus).

Monitoring should include checking for clinical and laboratory factors suggestive of intrauterine infection (professional consensus). No guidelines can be issued about the frequency of this monitoring (professional consensus). Adequate evidence does not exist to support a recommendation for or against the routine initiation of antibiotic therapy when the monitoring of an asymptomatic woman produces a single isolated positive result (e.g., elevated CRP, or hyperleukocytosis, or a positive vaginal sample) (professional consensus). In cases of intrauterine infection, the immediate intravenous administration (Grade B) of antibiotic therapy combining a beta-lactam with an aminoglycoside (Grade B) and early delivery of the child are both recommended (Grade A). Cesarean delivery of women with intrauterine infections is reserved for the standard obstetric indications (professional consensus). Expectant management is recommended for uncomplicated PROM before 37 weeks (Grade A), even when a sample is positive for Streptococcus B, as long as antibiotic prophylaxis begins at admission (professional consensus). Oxytocin and prostaglandins are two possible options for the induction of labor in women with PPROM (professional consensus).

Key words

Preterm premature rupture of the membranes, Premature rupture of the membranes before fetal viability, Antibiotic prophylaxis, Antenatal corticosteroids, Induction of labor

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1. Introduction

The sponsor (the French College of Gynecologists and Obstetricians (CNGOF)) appointed a steering committee (Appendix A) to define the exact questions to be put to the experts, to choose them, follow their work and draft the synthesis of recommendations resulting from their work [1]. The experts analyzed the scientific literature on the subject to answer the questions raised. A literature review identified the relevant articles through mid-2018 by searching the MEDLINE database and the Cochrane Library. The search was restricted to articles published in English and French. Priority was given to articles reporting results of original research, although review articles and commentaries were also consulted. Guidelines published by organizations or institutions such as the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Canadian Society of Gynecology and Obstetrics (SOGC), the National Institute for Health and Clinical Excellence (NICE) as well as previous guidelines published by the CNGOF were reviewed, and additional studies were located by reviewing bibliographies of identified articles. For each question, each overview of validated scientific data was assigned a level of evidence based on the quality of its data, in accordance with the framework defined by the HAS (French Health Authority), summarized below. Details on the systematic review process are provided in each article [2-8] dealing with the questions raised in the Content section.

1.1. Quality of evidence assessment

LE1: very powerful randomized comparative trials, meta-analysis of randomized comparative trials;

LE2: not very powerful randomized trial, well-run non-randomized comparative studies, cohort studies;

LE3: case-control studies;

LE4: non-randomized comparative studies with large biases, retrospective studies, cross-sectional studies, and case series.

A synthesis of recommendations was drafted by the organizing committee based on the replies given by the expert authors. Each recommendation for practice was allocated a grade, defined by the HAS as follows:

1.2. Classification of recommendations

Grade A: Recommendations are based on good and consistent scientific evidence

Grade B: Recommendations are based on limited or inconsistent scientific evidence

Grade C: Recommendations are based primarily on consensus and expert opinion

Professional consensus: In the absence of any conclusive scientific evidence, some practices have nevertheless been recommended on the basis of agreement between the members of the working group (professional consensus).

All texts were reviewed by persons not involved in the work, i.e., practitioners in the various specialties (Appendix) concerned and working in different situations (public, private, university or non-university establishments). Once the review was completed, changes were made, if appropriate, considering the assessment of the quality of the evidence.

The original long texts in French are cited [2-8], but their individual references are not included here in view of the enormous space they would occupy in this article intended to summarize the guidelines.

2. Epidemiology, risk factors, and the child's prognosis (2)

According to the 2016 French national perinatal survey, premature rupture of the membranes (PROM) before 37 weeks occurs in 2-3% of pregnancies, and PROM before 34 weeks in less than 1% (LE2). Its frequency increases as the pregnancy advances (LE2) and is higher in multiple than in singleton pregnancies (LE2). Most women give birth in the week that follows the rupture, and the duration of latency (defined as the interval between PROM and the birth) diminishes as gestational age at PROM rises (LE2). Many factors are associated with the prolongation (low gestational age) or shortening (multiple pregnancy, cervical

modifications, oligohydramnios, infection, placental detachment, or cord prolapse) of the latency period after preterm PROM.

The major risk factors for PPROM are a history either of it or of preterm delivery (LE3), cervical abnormalities before pregnancy (LE4), vaginal bleeding (LE4), cervical shortening during pregnancy (LE2), genital infections by chlamydiae and/or gonorrhea (LE3), and intrauterine infection (LE3). Most patients, however, present no risk factors (LE2). The risk of recurrence during subsequent pregnancies ranges from 6% to 17%, regardless of gestational age at the index PROM (LE3). No model for individual prediction of the risk of PPROM has been validated, and their use in clinical practice is not recommended (Grade B).

Preterm delivery and intrauterine infection (a term preferable to the overly imprecise chorioamnionitis [professional consensus]) are the major complications of PPROM (LE2). Other obstetric complications (such as cord prolapse or placental detachment) are rarer, but they too affect prognosis and therefore management (LE3). The risk of complications diminishes as gestational age at PROM rises (LE2). Regardless of the cause of delivery, gestational age at birth is the principal determinant of the preterm child's survival (LE2). Prolongation of the latency period is beneficial for the child (LE2).

At the same gestational age, the studies with the highest level of evidence do not show any excess risk of mortality for preterm births associated with PPROM, compared with those involving spontaneous labor with intact membranes (LE2). The risks of intraventricular hemorrhage, late neonatal bacterial infection, retinopathy of prematurity, or long-term cognitive disorders do not seem higher in cases of PPROM compared with other causes of preterm delivery (LE2). Higher risks of periventricular leukomalacia (LE2), early neonatal bacterial infection (LE2), bronchopulmonary dysplasia (LE2), or cerebral palsy (LE2) are found, although inconsistently, often in subgroups, perhaps explained by the differences in the choice of comparison group and of adjustment strategy.

Intrauterine infection is associated with an increased risk of in utero fetal death (LE3), early neonatal bacterial infection (LE2), and necrotizing enterocolitis (NEC) (LE2). Its association with the newborn's neurological morbidity remains controversial. Intrauterine infection is not

associated with a higher risk of neonatal mortality (LE4), sensory impairment (retinopathy of prematurity, blindness, deafness) (LE2), or bronchopulmonary dysplasia (LE2).

3. Diagnosis (3)

PROM is noticed most often by the discharge of amniotic fluid, easily recognizable. In these cases a laboratory diagnostic test is not required (professional consensus).

Ultrasound assessment of the quantity of amniotic fluid cannot either confirm or rule out the diagnosis of PROM (LE4). In uncertain clinical situations, an immunochromatographic test to detect Insulin-like Growth Factor-Binding Protein-1 (IGFBP-1) or Placenta Alpha 1-Microglobulin (PAMG-1) is recommended to diagnose PROM, although it has not been demonstrated that their use reduces either neonatal or maternal morbidity (professional consensus). These tests have better sensitivity and specificity than the other biochemical markers (LE3). If one of these tests is negative, PROM is very improbable (LE3). Moreover, a positive result on the IGFBP-1 or PAMG-1 must not be considered dispositive proof of PROM because of the risk of a false positive finding, especially when cervical modifications are also present (professional consensus).

4. Therapeutic management (excluding antibiotic therapy) (4)

The woman should be hospitalized at diagnosis of preterm PROM if the fetus has reached viability (professional consensus). Clinical examination aims to look for signs of intrauterine infection: fever, fetal tachycardia, uterine contractions, or purulent vaginal discharge (professional consensus). If a cervical evaluation seems necessary, an examination by speculum or a digital or ultrasound cervical examination can be performed (professional consensus). Cervical assessments should be limited, regardless of the method used (professional consensus).

Samples for a complete blood count, CRP assay, and urinary and vaginal bacteriological testing should be taken at admission, before the administration of any antibiotics (professional consensus). In cases of a positive vaginal culture, an antimicrobial

susceptibility test is recommended to guide the antibiotic therapy in case of intrauterine infection and early neonatal bacterial infection (professional consensus).

Ultrasound should be performed to determine the fetal position, locate the placenta, and estimate fetal weight and the quantity of residual amniotic fluid (professional consensus).

Antenatal corticosteroids should be administered if the fetus's gestational age is less than 34 weeks (Grade A) and magnesium sulfate if delivery is imminent before 32 weeks (Grade A).

In the absence of any demonstrated neonatal benefits, there is not sufficient evidence to recommend (or to recommend against) initial tocolysis for preterm PROM (Grade C). If tocolysis is prescribed, it should not continue longer than 48 hours (Grade C). There is no evidence to justify a recommendation either for or against vitamin supplementation (vitamin C and E) (professional consensus). Strict bed rest should not be recommended (professional consensus). For women with a cerclage at admission, there is not adequate evidence to recommend its removal or maintenance at admission (professional consensus). However, if clinical or laboratory signs suggest intrauterine infection, the cerclage should be immediately removed (professional consensus).

Women who are clinically stable after at least 48 hours of hospital monitoring can be managed at home (professional consensus). On the other hand, it is not possible to offer criteria for selecting women eligible for home management (professional consensus).

Monitoring should include checking for clinical and laboratory factors suggestive of intrauterine infection (professional consensus). No adequate evidence justifies guidelines about the frequency of this monitoring (professional consensus).

Finally, couples must be adequately informed of the situation and the information they receive should be adapted to the clinical course as it progresses. This information must be provided by an obstetrician and a pediatrician (professional consensus).

5. Choices and duration of antibiotic prophylaxis (5)

Antibiotic prophylaxis should be prescribed at admission for preterm PROM (Grade A), because it is associated with a reduction in neonatal morbidity and maternal (LE1).

Streptococcus agalactiae (group-B streptococci) and *Escherichia coli* are the principal infectious agents involved in early neonatal bacterial infection (LE3) and should be the target of the antibiotic prophylaxis (professional consensus).

Theoretical arguments indicate that amoxicillin (parenteral or oral) or third-generation cephalosporins (parenteral) can each be used alone, but they have not been evaluated for this indication (professional consensus). In older studies of uncertain external validity, given the evolution in bacterial ecology, erythromycin, both with and without amoxicillin (parenteral or oral), showed neonatal benefits (LE1). These substances can therefore be used (professional consensus). The following are not recommended as antibiotic prophylaxis: amoxicillin-clavulanic acid (professional consensus), aminoglycosides, glycopeptides, first- or second-generation cephalosporins, clindamycin, or metronidazole (professional consensus).

Antibiotic prophylaxis should be prescribed for a period of 7 days (Grade C). Nonetheless, as bacterial resistance develops after long treatments, stopping this antibiotic prophylaxis early appears acceptable, even though it has not been assessed in this situation of an initial vaginal sample that turned out to be negative (professional consensus). If the vaginal sample is positive at admission, adaptation of the antibiotic prophylaxis to the culture and to the antibiotic susceptibility testing must be discussed (professional consensus).

Routine repetition of antibiotic prophylaxis is not recommended during the latency period or when elevated CRP is the only sign, or when vaginal bacteria carriage is asymptomatic (professional consensus).

The literature includes no data about antibiotic prophylaxis during labor after preterm PROM in asymptomatic women. In this context, the French Society of Neonatology (SFN) has issued guidelines applicable to fetuses from 34 weeks of gestation.

6. Intrauterine infection: diagnosis and treatment (6)

Intrauterine infection can be clinically diagnosed when all of the following criteria are met (professional consensus):

Fever, defined by a maternal temperature equal to or greater than 38°C, confirmed after an interval of 30 minutes, with no nongynecologic infectious cause identified, associated with at least two of the following criteria:

- persistent fetal tachycardia > 160 bpm,
- uterine pain or painful uterine contractions or spontaneous labor,
- purulent amniotic fluid.

Maternal plasma CRP and hyperleukocytosis have limited value for the diagnosis of intrauterine infection (LE3). In asymptomatic women, a plasma CRP level less than 5 mg/l makes it possible to rule out the diagnosis (LE3). The plasma CRP assay is thus recommended for its negative predictive value (Grade C). The interpretation of maternal hyperleukocytosis results must not be interpreted too close in time to any corticosteroid therapy (professional consensus).

Bacteriological examination of the amniotic fluid, collected by amniocentesis, is not recommended for the diagnosis of intrauterine infection (professional consensus).

In cases of intrauterine infection, intravenous antibiotic therapy must be administered immediately to reduce the risks of maternal and neonatal infectious complications (Grade B).

It must be effective against *S. agalactiae* and *E. coli* (professional consensus). The spectrum can be expanded in cases of serious infection or when infection to resistant bacteria is suspected or documented (professional consensus). The antibiotic therapy must include a combination of a beta-lactam and an aminoglycoside (Grade B). The most appropriate aminoglycoside is gentamicin, by a daily intravenous injection (professional consensus).

Depending on the local bacteriological ecology, the results of prenatal samples, and maternal sepsis, the beta-lactam can be chosen from among amoxicillin, a third-generation cephalosporin, or, in cases of a serious allergy to beta-lactams, aztreonam (professional consensus). Aztreonam requires the addition of a substance that acts against gram-positive bacteria (professional consensus). For women with cesareans, the data are insufficient to recommend using (or not using) clindamycin or metronidazole to reduce the risk of postoperative infection by anaerobic bacteria (professional consensus).

The treatment must begin as soon as the infection is diagnosed and continue during labor (Grade B). In the postpartum period, a single supplementary dose is generally sufficient after vaginal delivery (professional consensus). Antibiotic use must be extended in the presence of a blood infection (professional consensus). The persistence of fever at 48 hours, obesity, or a cesarean delivery can also suggest prolongation of the treatment (professional consensus).

In cases of intrauterine infection identified after PROM, delivery of the child is recommended (Grade A). There is no proof that cesarean delivery is associated with an improvement of the neonatal prognosis, regardless of gestational age. Intrauterine infection alone does not justify cesarean delivery (professional consensus), which remains reserved for the standard obstetric indications (professional consensus).

7. Mode of delivery in the absence of complications (7)

Because a long latency period is not associated with an increased risk of neonatal complications before 34 weeks (LE3), it is recommended that labor not be induced for uncomplicated PROM (Grade C).

After 34 weeks of gestation, regardless of the gestational age at which PROM occurred, expectant management is associated with a higher frequency of intrauterine infection (LE2) but not of neonatal sepsis (LE1). An interventionist attitude is associated with higher rates of respiratory distress (LE2) and cesarean delivery (LE2), and with longer hospitalization in neonatal special care units (LE2). Expectant management is recommended for uncomplicated PROM before 37 weeks (Grade A), even when a sample is positive for *Streptococcus B*, as long as antibiotic prophylaxis begins at admission (professional consensus).

Oxytocin and prostaglandins are two possible options for the induction of labor in women with preterm PROM (professional consensus). The current data are too limited to enable a recommendation about the use of a transcervical balloon for this indication (professional consensus).

8. PROM before fetal viability (8)

Previaible PROM, that is, PROM before fetal viability, is rare, with a frequency ranging from 0.3% to 1% (LE4). After previable PROM, 50% to 60% of women nonetheless retain a satisfactory quantity of amniotic fluid (LE3), 23% to 53% give birth in the week after PROM, and slightly more than 35% of the women have not given birth 2 weeks after PROM (LE3). Oligohydramnios during the initial ultrasound is associated with a higher risk of a short latency period (LE4).

The frequency of medical terminations of pregnancy varies strongly between studies and depends especially on the laws of the country in which they occur (LE4). Hospital survival rates reported after various conservative treatments range from 17% to 55%, depending on the series (LE4), and survival without major morbidity ranges from 26% to 63% (LE4). Survival increases with gestational age at PROM and decreases when oligohydramnios is present (LE4). The perinatal prognosis of PROM depends largely on the extent of prematurity, especially for extremely preterm birth and its complications (LE3). Although at the same gestational age, neonatal mortality does not appear to be higher for previable PROM than for spontaneous preterm delivery (LE3), it nonetheless seems that neonatal and longer-term morbidity for the children born after 24 weeks of gestation is higher for preterm deliveries after previable PROM than for spontaneous preterm births that involved neither PROM nor induction of preterm birth (LE3).

The estimated frequency of pulmonary hypoplasia related to PROM ranges from 1.7% to 29% (LE4). The risk of pulmonary hypoplasia is associated with the earliness of PROM, the residual amniotic fluid volume, and the length of the latency period (LE4). No tool for the antenatal diagnosis of pulmonary hypoplasia currently exists (LE4).

The frequency of clinical intrauterine infection varies substantially between studies. For PROM before 24 weeks treated conservatively, it ranges from 16% to 71% (LE4). The frequency of maternal sepsis varies from 0.8% to 4.8% in the most recent studies, in which antibiotics were used routinely (LE4). Although the literature contains only one case report of

maternal death after previable PROM, French confidential enquiries into maternal deaths identified 3 cases between 2007 and 2012 (LE3).

Information is a component in its own right of the care to be provided to women with previable PROM and their partners. Parents must receive this information from physicians well aware of the risks associated with previable PROM and with the options for its management. Its contents must be appropriate to the situation and the potential developments and must cover both the prenatal and postnatal periods (professional consensus).

An initial period of hospitalization can be proposed to women with spontaneous previable PROM (professional consensus). Before fetal viability, this initial hospitalization need not occur in a level-3 referral perinatal center (professional consensus). Prophylactic antibiotic treatment is recommended, as described in section 4 (professional consensus).

The gestational age at which this treatment begins depends on the thresholds chosen for active care in the NICUs within maternity units and perinatal networks. It should consider most especially the parents' position (professional consensus). In view of the absence of any evidence that tocolysis is beneficial and the infectious risk associated with previable PROM, no recommendation is made about tocolysis in previable PROM (professional consensus).

In view of the prognostic importance of the quantity of amniotic fluid, its ultrasound evaluation can be proposed at the initial consultation and after a delay of 7 to 14 days if the delivery has not taken place (professional consensus).

Termination of pregnancy can take place at "any point during the pregnancy" in accordance with the strict conditions set forth by the Public Health Code article L2213-1, "either the continuation of the pregnancy seriously threatens the woman's health, or there is a strong probability that the child to be born is affected by a very severe condition recognized as incurable at the time of diagnosis." Accordingly, the provision of information must begin from the diagnosis of PROM and concern intrauterine infections that suggest the development of severe maternal sepsis so that the doctor can, should overt infection develop and in the absence of spontaneous labor, begin a discussion of elective abortion that can be performed

in a delay appropriate to the clinical situation and laboratory results (professional consensus). In this situation, the opinion of the multidisciplinary center of prenatal diagnosis (CPDPN) is not necessary, but the attestation must be signed by 4 persons including at least one expert physician on an official CPDPN list.

In the absence of elements likely to threaten the mother's health, the child's prognosis can lead the CPDPN to accept the mother's request to terminate the pregnancy. All situations, however, are not equivalent in terms of prognosis. Some factors have a major prognostic weight. These include gestational age at PROM, its spontaneous or induced nature, and oligohydramnios at 7 and/or 14 days after PROM. It is thus therefore important to focus on assessing these prognostic factors and not to rush a possible request in the absence of an emergency motivated by a threat to the mother's health.

After the initial hospitalization, there is no evidence on which to base a recommendation for further hospital management rather than return home, as long as there is no clinical or laboratory evidence of intrauterine infection (professional consensus).

Cases of previable PROM that follow amniocentesis have a better prognosis than spontaneous previable PROM (LE3). In the absence of research to define management in these cases of iatrogenic PROM, no guidelines can be issued for them.

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Appendix A

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