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

4

5 Thomas Schmitz^{1, 2, 3}, Loïc Sentilhes⁴, Elsa Lorthe^{3, 5}, Denis Gallot^{6, 7}, Hugo Madar⁴, Muriel
6 Doret-Dion⁸, Gaël Beucher⁹, Caroline Charlier^{10, 11, 12}, Charles Cazanave^{13, 14}, Pierre
7 Delorme^{3, 11, 15}, Charles Garabédian^{16, 17}, Elie Azria^{3, 11, 18}, Véronique Tessier^{15, 19}, Marie-
8 Victoire Sénat^{20, 21}, Gilles Kayem^{3, 22, 23}.

9

10 ¹Service de Gynécologie Obstétrique, Hôpital Robert Debré, AP-HP, Paris, France

11 ²Université Paris Diderot, Paris, France

12 ³Inserm UMR 1153 Equipe de recherche en Epidémiologie Obstétricale, Périnatale et
13 Pédiatrique (EPOPé), Centre de Recherche Epidémiologie et Statistique Sorbonne Paris
14 Cité, Paris, France

15 ⁴Service de Gynécologie-Obstétrique, Centre Hospitalier Universitaire de Bordeaux, Hôpital
16 Pellegrin, Bordeaux, France

17 ⁵EPIUnit – Institute of Public Health, University of Porto, Rua das Taipas, n°135, 4050-600
18 Porto, Portugal

19 ⁶Pôle Femme Et Enfant, CHU Estaing, Clermont-Ferrand, France

20 ⁷R2D2-EA7281, Université d'Auvergne, Faculté de Médecine, Clermont-Ferrand, France

21 ⁸Service de gynécologie obstétrique, hospices civils de Lyon, hôpital Femme-Mère-Enfant,
22 Bron, France

23 ⁹Service de Gynécologie Obstétrique et Médecine de la Reproduction, CHU de Caen,
24 France

25 ¹⁰Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants malades, AP-HP,
26 Paris France

27 ¹¹Université Paris Descartes, Paris, France

- 28 ¹²Centre d'Infectiologie Necker-Pasteur, Institut IMAGINE, France
- 29 ¹³Service des Maladies Infectieuses et Tropicales, Groupe Hospitalier Pellegrin, CHU de
30 Bordeaux, Bordeaux, France
- 31 ¹⁴Université de Bordeaux, USC EA 3671, Infections humaines à mycoplasmes et à
32 chlamydiae, Bordeaux, France
- 33 ¹⁵DHU Risques et Grossesse, Maternité Port Royal, Hôpitaux Universitaires Paris Centre,
34 Hôpital Cochin, AP-HP, Paris, France
- 35 ¹⁶CHU Lille, Hôpital Jeanne de Flandre, Clinique d'obstétrique, Lille, France
- 36 ¹⁷Université de Lille, EA 4489 – Environnement périnatal et croissance, Lille, France
- 37 ¹⁸Maternité Notre Dame de Bon Secours, Groupe Hospitalier Paris Saint-Joseph, DHU
38 Risques et Grossesse, Paris, France
- 39 ¹⁹Collège National des Sages-Femmes
- 40 ²⁰Service de Gynécologie Obstétrique, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France
- 41 ²¹Université Paris-Sud, Université de Médecine Paris-Saclay, Le Kremlin-Bicêtre, France
- 42 ²²Service de Gynécologie Obstétrique, Hôpital Trousseau, AP-HP, Paris, France
- 43 ²³Université Pierre et Marie Curie, Paris, France

44

45 Correspondence:

46 Pr Thomas Schmitz

47 Service de Gynécologie-Obstétrique, Hôpital Robert Debré

48 48 Bd Sérurier, 75019 Paris, France

49 E-Mail : thomas.schmitz@aphp.fr

50

51 **Abstract**

52 In France, the frequency of premature rupture of the membranes (PROM) is 2% to 3% before
53 37 weeks' gestation (level of evidence [LE] 2) and less than 1% before 34 weeks (LE2).
54 Preterm delivery and intrauterine infection are the major complications of preterm PROM
55 (PPROM) (LE2). Prolongation of the latency period is beneficial (LE2). Compared with other
56 causes of preterm delivery, PPRM is associated with a clear excess risk of neonatal
57 morbidity and mortality only in cases of intrauterine infection, which is linked to higher rates
58 of in utero fetal death (LE3), early neonatal infection (LE2), and necrotizing enterocolitis
59 (LE2).

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

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

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

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

93

94 **Key words**

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

97

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99	
100	1. Introduction
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109 **1. Introduction**

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

128

129 1.1. Quality of evidence assessment

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

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

134 LE3: case-control studies;

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

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

140

141 1.2. Classification of recommendations

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

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

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

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

148

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

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

156

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

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

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

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

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

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

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

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

195

196 **3. Diagnosis (3)**

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

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

209

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

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

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

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

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

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

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

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

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

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

245

246 **5. Choices and duration of antibiotic prophylaxis (5)**

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

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

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

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

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

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

272

273 **6. Intrauterine infection: diagnosis and treatment (6)**

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

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

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

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

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

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

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

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

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

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

315

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

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

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

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

332 **8. PROM before fetal viability (8)**

333 Previably PROM, that is, PROM before fetal viability, is rare, with a frequency ranging from
334 0.3% to 1% (LE4). After previable PROM, 50% to 60% of women nonetheless retain a
335 satisfactory quantity of amniotic fluid (LE3), 23% to 53% give birth in the week after PROM,
336 and slightly more than 35% of the women have not given birth 2 weeks after PROM (LE3).
337 Oligohydramnios during the initial ultrasound is associated with a higher risk of a short
338 latency period (LE4).

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

351 The estimated frequency of pulmonary hypoplasia related to PROM ranges from 1.7% to
352 29% (LE4). The risk of pulmonary hypoplasia is associated with the earliness of PROM, the
353 residual amniotic fluid volume, and the length of the latency period (LE4). No tool for the
354 antenatal diagnosis of pulmonary hypoplasia currently exists (LE4).

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

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

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

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

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

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

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

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

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

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

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

404

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428

429 **Appendix A**

430

431 **Sponsor**

432 CNGOF (French national college of gynecologists and obstetricians, Collège national des
433 gynécologues et obstétriciens français)

434 91 boulevard de Sébastopol – 75002 Paris

435

436 **Steering committee**

437 G. Kayem, president (gynecologist-obstetrician, UHC, Paris), T. Schmitz, coordinator
438 (gynecologist-obstetrician, UHC, Paris, CNGOF), L. Sentilhes (gynecologist-obstetrician,
439 UHC, Bordeaux, CNGOF), M.V. Senat (gynecologist-obstetrician, UHC, Le Kremlin-Bicêtre,
440 CNGOF), V. Tessier (CNSF, National College of French Midwives)

441

442 **Working group experts**

443 E. Azria (gynecologist-obstetrician, ESPIC, Paris), G. Beucher (gynecologist-obstetrician,
444 UHC, Caen), C. Cazanave (Infectious disease specialist, UHC, Bordeaux), C. Charlier
445 (Infectious disease specialist, UHC, Paris), P. Delorme (gynecologist-obstetrician, UHC,
446 Paris), M. Doret-Dion (gynecologist-obstetrician, UHC, Bordeaux), D. Gallot (gynecologist-
447 obstetrician, UHC, Clermont-Ferrand), C. Garabédian (gynecologist-obstetrician, UHC, Lille),
448 E. Lorthe (Midwife, INSERM, Paris), H. Madar (gynecologist-obstetrician, UHC, Bordeaux)

449

450 **Reviewers**

451 P. Berveiller (Gynecologist-Obstetrician, Intercommunal Hospital Center, Poissy), P. Boileau
452 (Pediatrician-Neonatologist, Intercommunal Hospital Center, Poissy, Poissy), G. Carlesl
453 (Gynecologist-Obstetrician, Community hospital center, Saint-Laurent du Maroni), F.
454 Coatleven (Gynecologist-Obstetrician, UHC, Bordeaux), A. Delabaere (gynecologist-
455 obstetrician, UHC, Clermont-Ferrand), P. Deruelle (Gynecologist-Obstetrician, UHC, Lille), F.
456 Desvignes (Gynecologist-Obstetrician, Community hospital center, Vichy), P. Dolley
457 (Gynecologist-Obstetrician, UHC, Caen), M. Dreyfuss (Gynecologist-Obstetrician, UHC,
458 Caen), F. Fuchs (Gynecologist-Obstetrician, UHC, Montpellier), F. Goffinet (Gynecologist-
459 Obstetrician, UHC, Paris), E. Grossetti (Gynecologist-Obstetrician, Community hospital
460 center, Le Havre), I. Rennes-Guellec (Pediatrician-Neonatologist, UHC, Paris), P. Guerby
461 (Gynecologist-Obstetrician, UHC, Toulouse), A.C. Jambon (Gynecologist-Obstetrician,
462 Community hospital center, Tourcoing), J.M. Jouannic (Gynecologist-Obstetrician, UHC,
463 Paris), C. Le Ray (Gynecologist-Obstetrician, UHC, Paris), O. Lesens (Infectious disease
464 specialist, UHC, Clermont-Ferrand), V. Letouzey (Gynecologist-Obstetrician, UHC, Nîmes),
465 L. Marcellin (Gynecologist-Obstetrician, UHC, Paris), JP. Rasigade (Infectious disease
466 specialist, UHC, Lyon), P. Rozenberg (Gynecologist-Obstetrician, Intercommunal hospital
467 center, Poissy), N. Sananès (Gynecologist-Obstetrician, UHC, Strasbourg), D. Tardif
468 (Gynecologist-Obstetrician, Community hospital center, Annecy Gennevois), H. Torchin
469 (Pediatrician-Neonatologist, UHC, Paris), R. Verdon (Infectious disease specialist, UHC,
470 Caen), S. Vigoureux (Gynecologist-Obstetrician, UHC, Le Kremlin-Bicêtre), N. Winer
471 (Gynecologist-Obstetrician, UHC, Nantes)