



Setting standards to improve women's health

PRETERM PRELABOUR RUPTURE OF MEMBRANES

This is the first edition of the guideline.

1. Purpose and scope

The aim of this guideline is to make recommendations relating to the diagnosis, investigation and management of women with preterm prelabour rupture of the membranes (PPROM). The guideline evaluates various antenatal tests in helping to predict the fetus at risk from intrauterine infection. The role of prophylactic antibiotics, steroids and tocolytic agents and the optimum gestation to deliver women with pregnancies complicated by PPRM is examined and recommendations are provided based on published evidence.

2. Background

PPROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries and can result in significant neonatal morbidity and mortality.¹⁻³ The three causes of neonatal death associated with PPRM are prematurity, sepsis and pulmonary hypoplasia. Women with intrauterine infection deliver earlier than non-infected women and infants born with sepsis have a mortality rate four times higher than those without sepsis.⁴ In addition, there are maternal risks associated with chorioamnionitis.

There is evidence demonstrating an association between ascending infection from the lower genital tract and PPRM. In women with PPRM about one-third of pregnancies have positive amniotic fluid cultures^{5,6} and studies have shown that bacteria have the ability to cross intact membranes.^{7,8}

3. Identification and assessment of evidence.

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, DARE and EMBASE), TRIP, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published between 1966 and 2005. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'preterm prelabour rupture of membranes', 'amnioinfusion', 'sealing amniotic membranes', 'intra-amniotic infection', 'Nitrazine', 'fetal fibronectin', 'amniocentesis', 'antenatal corticosteroids', and 'tocolytics' and the search limited to humans and English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

4. How is the diagnosis of PPROM best achieved?

The diagnosis of spontaneous rupture of the membranes is best achieved by maternal history followed by a sterile speculum examination.

B

Ultrasound examination is useful in some cases to help confirm the diagnosis.

C

Digital examination should be avoided where PPROM is suspected.

C

The diagnosis is made by a history suggestive of spontaneous rupture of membranes (SROM) followed by a sterile speculum examination demonstrating pooling of fluid in the posterior vaginal fornix; a Nitrazine test is not necessary. Ultrasound examination demonstrating oligohydramnios is also used to help confirm the diagnosis of spontaneous rupture of the membranes.⁹⁻¹²

Digital vaginal examination is best avoided unless there is a strong suspicion that the woman may be in labour. This is because micro-organisms may be transported from the vagina into the cervix, leading to intrauterine infection, prostaglandin release and preterm labour. A retrospective study reported that the latency interval between SROM and delivery in those who had a digital vaginal examination was significantly shorter than if a sterile speculum examination only was performed.¹³

Evidence level IIb

A series of tests have been used to confirm membrane rupture; the most widely used has been the Nitrazine test, which detects pH change,^{14,15} which has a sensitivity of 90% and a false positive rate of 17%.¹⁶ More recently, other tests have been evaluated in the diagnosis of ruptured membranes and fetal fibronectin and raised insulin-like growth factor binding protein-1 in cervical/vaginal secretions have reported sensitivities of 94% and 75% and specificities of 97%, respectively.^{17,18}

5. What antenatal tests should be performed?

Women should be observed for signs of clinical chorioamnionitis at least 12-hourly.

✓

A weekly high vaginal swab and at least a weekly maternal full blood count should be considered.

✓

Fetal monitoring using cardiotocography should be considered where regular fetal surveillance is required.

C

Biophysical profile scoring or Doppler velocimetry should not be considered as first-line surveillance or diagnostic tests for fetal infection.

B

The criteria for the diagnosis of clinical chorioamnionitis include maternal pyrexia, tachycardia, leucocytosis, uterine tenderness, offensive vaginal discharge and fetal tachycardia. During inpatient observation, the woman should be regularly examined for such signs of intrauterine infection and an abnormal parameter or a combination of them may indicate intrauterine infection. The frequency of maternal temperature, pulse and fetal heart rate auscultation should be between 4 hours and 8 hours.^{9,10,19}

Maternal pyrexia (above 37.8°C), offensive vaginal discharge and fetal tachycardia (rate above 160 beats/minute) indicate clinical chorioamnionitis. There is a variation in the literature regarding the accuracy of the laboratory tests of leucocytosis and raised C-reactive protein in the prediction of chorioamnionitis. The sensitivities and false positive rates for leucocytosis in the detection of clinical chorioamnionitis range from 29-47% and 5-18%, respectively.^{9,19} The specificity of C-reactive protein is 38-55%.^{9,20,21} Although weekly culture of swabs from the vagina are often taken as part of the clinical management of women with PPROM, the data evaluating this practice do not show conclusively that it is beneficial. It has been shown that positive genital tract cultures predict 53% of positive amniotic fluid cultures with a false-positive rate of 25%.²² However, the presence of leucocytosis may be useful clinically in cases where there is doubt about the diagnosis of

Evidence level IIa

chorioamnionitis. Furthermore, high vaginal swabs may indicate group B streptococcus, which provides the opportunity for intrapartum antibiotic therapy.

Abnormal biophysical profile scores and increased systolic/diastolic ratios in the umbilical artery have been shown to be markers of intrauterine infection.²³ The true and false positive rates for an abnormal biophysical profile score in the prediction of clinical chorioamnionitis range from 25–80% and 2–9%, respectively.^{24–29} Another dataset using positive amniotic fluid and positive fetal blood cultures as endpoints for infection found that the biophysical profile score or Doppler studies of the placental or fetal circulation did not provide accurate distinction between infected and noninfected cases.^{11,30} Fetal tachycardia predicts 20–40% of cases of intrauterine infection with a false-positive rate of about 3%.^{9,11,31} Cardiotocography is useful because a fetal tachycardia, if present, may represent a late sign of infection and is frequently used in the clinical definition of chorioamnionitis in studies.

Evidence level IIa

There are no randomised controlled trials to support the premise that pregnancy outcome is improved by the use of frequent biophysical or Doppler assessment. The disparity in the literature evaluating these noninvasive tests of fetal wellbeing suggests that, although some studies have shown benefit, overall the tests are of limited value in differentiating between fetuses with and without infection.

5.1 *What is the role of amniocentesis?*

Routine amniocentesis is not recommended for women with PPROM.

B

Intrauterine infection, as defined by positive amniotic fluid cultures, is found in 36% of women with PPROM. Most infections are subclinical without obvious signs of chorioamnionitis.⁵ Positive amniotic fluid cultures increase the risks of preterm delivery, neonatal sepsis, respiratory distress syndrome, chronic lung disease, periventricular leukomalacia, intraventricular haemorrhage and cerebral palsy.^{32–34}

Current evidence suggests that infection is a cause rather than a consequence of amniorrhexis.³⁵ Amniocentesis has the potential to detect subclinical infection before the onset of maternal signs of chorioamnionitis and before the onset of fetal sepsis, allowing appropriate intervention such as administration of antibiotics in infected cases and/or delivery, depending on the gestation, and expectant management for women with negative amniotic fluid cultures. Rapid tests on amniotic fluid such as Gram stain and assay of cytokines such as interleukins 6 and 18, which indicate intrauterine infection, may be performed.^{34,36,37}

Evidence level IIa

Although prophylactic antibiotic therapy in cases of PPROM has been shown to have benefits, proponents for clinical management using amniocentesis argue that treatment should be targeted to appropriate women because a potential adverse effect of prolonged antibiotic therapy in PPROM includes superinfection with virulent organisms.³⁸ It remains to be determined in future studies whether amniocentesis improves outcomes. Amniocentesis should be performed in specialised units.

Although there are data documenting an association between subclinical intrauterine infection and adverse neonatal outcome, the role of amniocentesis in improving outcome remains to be determined.

6. Management

6.1 *Are prophylactic antibiotics recommended?*

Erythromycin (250 mg orally 6 hourly) should be given for 10 days following the diagnosis of PPROM.

A

Co-amoxiclav is not recommended for women with PPROM because of concerns about necrotising enterocolitis.

A

Twenty-two trials involving over 6000 women with PPROM before 37 weeks were included in a meta-analysis.³⁹ The use of antibiotics following PPROM was associated with a statistically significant reduction in chorioamnionitis (RR 0.57; 95% CI 0.37–0.86). There was a significant reduction in the numbers of babies born within 48 hours (RR 0.71; 95% CI 0.58–0.87) and seven days (RR 0.80; 95% CI 0.71–0.90). Neonatal infection was significantly reduced in the babies whose mothers received antibiotics (RR 0.68; 95% CI 0.53–0.87). There was also a significant reduction in the number of babies with an abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82; 95% CI 0.68–0.98). There was no significant reduction in perinatal mortality although there was a trend for reduction in the treatment group.

Evidence level Ia

There was a variation in the choice of antibiotics used and the duration of therapy in the studies examined in the meta-analysis.³⁹ Ten trials tested broad-spectrum penicillin, either alone or in combination, five tested macrolide antibiotics (erythromycin) either alone or in combination and one trial tested clindamycin and gentamycin. The duration of treatment varied between two doses and 10 days. Any penicillin (except co-amoxiclav) or erythromycin versus placebo was associated with a significant reduction in the numbers of babies born within 48 hours and who had positive blood cultures. Co-amoxiclav versus placebo was associated with an increase in the numbers of babies born with necrotising enterocolitis.

If group B streptococcus is isolated in cases of PPROM, antibiotics should be given in line with the recommendation for routine intrapartum prophylaxis in the RCOG Green-top Guideline No. 36: *Prevention of Early Onset Neonatal Group B Streptococcal Disease*.⁴

6.2 What is the role of antenatal corticosteroids?

Antenatal corticosteroids should be administered in women with PPROM.

A

A meta-analysis of 15 randomised controlled trials involving more than 1400 women with preterm rupture of the membranes demonstrated that antenatal corticosteroids reduced the risks of respiratory distress syndrome (RR 0.56; 95% CI 0.46–0.70), intraventricular haemorrhage (RR, 0.47; 95% CI 0.31–0.70) and necrotising enterocolitis (RR 0.21; 95% CI 0.05–0.82). They do not appear to increase the risk of infection in either mother (RR 0.86; 95% CI 0.61–1.20) or baby (RR 1.05; 95% CI 0.66–1.68).⁴¹

Evidence level Ia

As stated in the RCOG Green-top Guideline No. 7,⁴² indications for antenatal corticosteroid therapy include women with PPROM between 24 and 34 weeks of gestation.

6.3 Tocolysis. Should tocolytic agents be used?

Prophylactic tocolysis in women with PPROM without uterine activity is not recommended.

A

Women with PPROM and uterine activity who require intrauterine transfer or antenatal corticosteroids should be considered for tocolysis.



6.3.1 Prophylactic tocolysis

Three randomised studies of a total of 235 women with PPROM reported that the proportion of women remaining undelivered 10 days after membrane rupture was not significantly higher in those receiving tocolysis compared with those receiving none.^{43–45}

Evidence level Ib

A recent retrospective case-control study showed that tocolysis after PPROM did not increase the interval between membrane rupture and delivery or reduce neonatal morbidity.⁴⁶

Evidence
level IIa

6.3.2 Therapeutic tocolysis

A randomised trial involving 30 women demonstrated that delivery can be inhibited for 24 hours by intravenous ritodrine.⁴⁷ After 24 hours there was no difference in the duration of pregnancy in either group. A randomised study involving 109 women showed that, for preterm labour associated with preterm rupture of the membranes after 28 weeks of gestation, there were no significant differences between treatment groups in intrauterine time after the onset of regular contractions.⁴⁸ The results of another randomised study of 79 women with contractions following PPROM did not suggest that there is benefit to tocolysis in terms of prolonging the interval to delivery or in reducing perinatal morbidity or mortality.⁴⁹ A recent case-control study involving 193 women found that aggressive tocolysis after PPROM did not increase latency or decrease neonatal morbidity compared with either limited tocolysis or no tocolysis at all.¹²

Tocolytic treatment for women in preterm labour was the subject of the RCOG Clinical Guideline No. 1 (B): *Tocolytic Drugs for Women in Preterm Labour*.⁵⁰

In the absence of clear evidence that tocolysis improves neonatal outcome following PPROM, it is reasonable not to use it. It is possible that tocolysis could have adverse effects, such as delaying delivery from an infected environment, since there is an association between intrauterine infection, prostaglandin and cytokine release and delivery. However, the benefits of antenatal steroids apply equally to women with PPROM and, in some clinical circumstances, the risk-benefit ratio may lead to consideration of tocolysis for this purpose. Similarly it would seem wise to consider tocolysis for transfer of women, depending on individual circumstances.

7. Amnioinfusion

Should amnioinfusion in labour be carried out?

Transvaginal amnioinfusion in labour is not recommended for women with preterm rupture of membranes.

A

Transabdominal amnioinfusion is not recommended as a method of preventing pulmonary hypoplasia in very preterm PPROM.

B

Transvaginal amnioinfusion during labour has been the subject of a Cochrane review⁵¹ where one randomised controlled trial involving 66 women with SROM between 26 and 35 weeks of gestation and who received amnioinfusion during labour was examined.⁵² The results showed no significant differences between amnioinfusion and no amnioinfusion for caesarean section, low Apgar scores and neonatal death. The implication for practice is that there is insufficient evidence to guide clinical practice concerning the use of amnioinfusion.

Evidence
level Ib

A recently published trial of 65 women with PPROM between 24 and 33 weeks of gestation who were randomised to transabdominal amnioinfusion or expectant management showed that the risk of postnatal death from pulmonary hypoplasia was similar in both groups.⁵³

Another case-control study involving 24 women reported no difference in the incidence of pulmonary hypoplasia between controls and treated women.⁵⁴

Evidence
level Ib

One other recent study involving 71 women with PPROM before 26 weeks of gestation demonstrated that the percentage of intrauterine fetal survival was higher in treated than in controlled groups (64.8% versus 32.3%, $P < 0.01$).⁵⁵

Evidence
level IIa

At present, there is insufficient evidence to recommend this treatment outside randomised trials. There is presently a randomised controlled trial comparing expectant management with serial amnioinfusions in women with early second trimester PPROM.⁵⁶

8. Use of fibrin glue

What is the role of fibrin glue in the sealing of chorioamniotic membranes to prevent pulmonary hypoplasia?

Fibrin sealants are not recommended as routine treatment for second-trimester oligohydramnios caused by PPROM.

B

There are publications involving small patient numbers with midtrimester PPROM describing transvaginal or transabdominal injection of fibrin into the amniotic fluid with the aim of sealing the membranes.⁵⁷⁻⁵⁹ The 'amniopatch' resulted in an increase in amniotic fluid volume in some cases. Larger studies are needed when examining neonatal outcome before this treatment can be recommended as routine practice.

Evidence level III

9. Outpatient monitoring

Can patients be monitored at home?

Women should be considered for outpatient monitoring of PPROM only after rigorous individual selection by a consultant obstetrician.

B

Outpatient monitoring should be considered only after a period of 48–72 hours of inpatient observation



Women should be advised of the signs and symptoms of chorioamnionitis and under what circumstances they should seek specialist advice.



Women being monitored at home for PPROM should take their temperature twice daily or should be advised of the symptoms associated with infection.



There should be clearly described local arrangements for the frequency of outpatient visits and what should be carried out at these visits.



In a randomised study of home versus hospital management outcomes, the two groups were comparable with a similar latency period and gestational age at delivery.¹⁰ There were no significant differences in the frequencies of chorioamnionitis, respiratory distress syndrome or neonatal sepsis. However, only 18% of the women were eligible and agreed to randomisation. The women were randomised after 72 hours in hospital and 57–74%, respectively, in the home and the hospital groups had an amniocentesis for Gram stain and culture. This study does not support routine home management in women with PPROM but supports rigorous individual selection of women for this treatment.

There are insufficient data to make recommendations of home, daycare and outpatient monitoring rather than continued hospital admission in women with PPROM. It would be considered reasonable to maintain the woman in hospital for at least 48 hours before a decision is made to allow her to go home. This method of management should be individualised and restricted to certain groups of women. Women should be instructed to take regular temperature recordings at home every 12 hours or to be aware of the symptoms associated with infection.

Evidence level III

10. Delivery of the fetus

When is the appropriate time to deliver?

Delivery should be considered at 34 weeks of gestation.

B

Where expectant management is considered beyond 34 weeks of gestation, women should be counselled about the increased risk of chorioamnionitis and its consequences versus the decreased risk of serious respiratory problems in the neonate, admission for neonatal intensive care and caesarean section.

B

Many studies have demonstrated benefits in conservative management for gestations of less than 34 weeks, whereas the management of pregnancies complicated by PPROM between 34 and 37 weeks of gestation continues to be a contentious issue.⁶⁰

A recent retrospective study examining 430 women with PPROM demonstrated that composite neonatal minor morbidity such as hyperbilirubinaemia and transient tachypnoea of the newborn was significantly higher among pregnancies delivered at 34 weeks of gestation or less as compared with those delivered at 36 weeks.⁶¹ Composite major neonatal morbidity, including respiratory distress syndrome and intraventricular haemorrhage, was significantly higher among pregnancies delivered at 33 weeks of gestation or less as compared with those delivered at 36 weeks. There was no difference in the major morbidity rates for those pregnancies delivered beyond 34 weeks. The authors' conclusion was that expectant management at 34 weeks and beyond is of limited benefit.

Evidence level III

A randomised trial assigning 93 women with PPROM between 32 weeks and 36 weeks and 6 days of gestation either to immediate or delayed delivery showed that the incidence of respiratory distress syndrome, intraventricular haemorrhage and confirmed neonatal sepsis was not significantly different in the two groups.⁶² Although, in the expectantly managed group, the 27.7% incidence of chorioamnionitis was higher than the 10.9% in the induced group, this difference did not reach statistical significance.

In another report, 129 women with PPROM between 30 weeks and 34 weeks of gestation were randomly assigned to either immediate delivery or expectant management.⁶³ The mean gestational age at delivery was 31.7 weeks in the immediate delivery group and 32 weeks in that managed expectantly. Although the incidence of chorioamnionitis was significantly less in the immediate delivery group (2%) as compared with the expectant management group (15%; $P < 0.05$), there were no significant differences between the groups with regard to neonatal morbidity.

Evidence level Ib

In a prospective randomised study of 120 women with PPROM between 34 weeks and 37 weeks of gestation, the expectantly managed group had a higher incidence of chorioamnionitis (16%) compared with the immediate delivery group (2%, $P < 0.05$). The incidence of sepsis was 5% in the expectantly managed group and 0% in the immediate delivery group but this was not statistically significant. There was no difference in the risk of respiratory distress syndrome.⁶⁰

A retrospective series examining neonatal outcome following cases with PPROM between 32 weeks and 36 weeks showed that the specific gestation for reduced morbidity was 34 weeks.⁶⁴ The incidence of respiratory distress syndrome and the length of hospital stay were reduced in infants delivered after 34 weeks of gestation. The incidence of respiratory distress syndrome was 22.5% and 5.8% at 33 and 34 weeks, respectively. Although the incidence beyond 34 weeks was relatively low, the condition affected infants into the 36th week, with incidences of 10.4–1.5% at 35 and 36 weeks, respectively.

Data from existing studies call for further research to elucidate the optimal delivery gestational age for women

with PPROM between 34 weeks and 37 weeks of gestation. There are currently two ongoing randomised controlled trials comparing intentional delivery versus conservative management in women with PPROM between 32 weeks and 35 weeks: Lacaze-Masmonteil T, Chari R, University of Alberta; Clinical Trials.gov identifier NCT00259519⁶⁵ and Morris J, Royal North Shore Hospital, Australia, ISRCTN 44485060.⁶⁶ Details of the trials can be found at: www.clinicaltrials.gov/ct/show/.

Until then, published data question the benefit of continued expectant management beyond 34 weeks of gestation. There is little evidence that intentional delivery after 34 weeks adversely affects neonatal outcome. There is a suggestion from these studies that expectant management beyond 34 weeks is associated with an increased risk of chorioamnionitis.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	Good practice point
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

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unless otherwise indicated