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Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24^{+0} Weeks of Gestation

Green-top Guideline No. 73

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Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24^{+0} Weeks of Gestation

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1. Key recommendations

- The diagnosis of spontaneous rupture of the membranes is made by maternal history followed by a sterile speculum examination. [Grade D]
- If, on speculum examination, no amniotic fluid is observed, clinicians should consider performing an insulin-like growth factor-binding protein 1 (IGFBP-1) or placental alpha microglobulin-1 (PAMG-1) test of vaginal fluid to guide further management. [Grade B]
- Following the diagnosis of preterm prelabour rupture of the membranes, (PPROM) an antibiotic (preferably erythromycin) should be given for 10 days or until the woman is in established labour (whichever is sooner). [Grade A]
- Women who have PPROM between 24^{+0} and 33^{+6} weeks' gestation should be offered corticosteroids; steroids can be considered up to 35^{+6} weeks' gestation. [Grade A]
- A combination of clinical assessment, maternal blood tests (C-reactive protein and white cell count) and fetal heart rate should be used to diagnose chorioamnionitis in women with PPROM; these parameters should not be used in isolation. [Grade D]
- Women whose pregnancy is complicated by PPROM after 24^{+0} weeks' gestation and who have no contraindications to continuing the pregnancy should be offered expectant management until 37^{+0} weeks; timing of birth should be discussed with each woman on an individual basis with careful consideration of patient preference and ongoing clinical assessment. [Grade A]
- In women who have PPROM and are in established labour or having a planned preterm birth within 24 hours, intravenous magnesium sulfate should be offered between 24^{+0} and 29^{+6} weeks of gestation. [Grade A]

2. Background and scope

Preterm prelabour rupture of membranes (PPROM) complicates up to 3% of pregnancies and is associated with 30–40% of preterm births.[1] PPROM can result in significant neonatal morbidity and mortality, primarily from prematurity, sepsis, cord prolapse and pulmonary hypoplasia. In addition, there are risks associated with chorioamnionitis and placental abruption.[2]

The median latency after PPROM is 7 days and tends to shorten as the gestational age at PPROM advances.[3,4]

This guideline comprises recommendations relating to the diagnosis, assessment, care and timing of birth of women presenting with suspected PPROM from 24^{+0} to 36^{+6} weeks of gestation. It also addresses care in a subsequent pregnancy. An infographic and audio version to supplement this guideline are available online (Infographic S1,

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Audio S1). It supplements NICE guideline (NG25), *Preterm labour and birth* (published November 2015).[5] Relevant recommendations can also be found in the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline [GTG no. 36], *Early-onset of Group B Streptococcal Disease*.[6]

3. Identification and assessment of evidence

The Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed) were searched looking for the following terms in the title or abstract 'preterm prelabour rupture of membranes', 'amnioinfusion', 'chorioamnionitis,' 'intra-amniotic infection', 'IGFBP-1', 'PAMG-1', 'amniocentesis', 'antenatal corticosteroids' and 'tocolytics'. The search was restricted to articles published until January 2019. The full search strategy is available to view online as supporting information (Appendix S1 and S2).

This guideline was developed using the methodology described in Clinical Governance Advice 1 (a-c).[7]

4. Diagnosis

4.1 How is the diagnosis of PPROM made?

Recommendation	Evidence Level	Strength	Rationale for the recommendation
The diagnosis of spontaneous rupture of the membranes is made by maternal history followed by a sterile speculum examination demonstrating liquor	**4**	**D**	Given that this is the 'gold standard', further trials are unlikely to add to the evidence for this recommendation
If, on speculum examination, no amniotic fluid is observed, clinicians should consider performing an IGFBP-1 or PAMG-1 test of vaginal fluid to guide further management	**2++**	**B**	Recommended in NG25.[5] Studies have reported high levels of sensitivity and specificity for these markers
The role of ultrasound assessment of amniotic fluid volume is unclear	**4**	✓	No specific studies identified in the role of liquor volume in supporting the diagnosis of PPROM

The presence of a pool of fluid in the vagina at sterile speculum examination is highly suggestive of membrane rupture, and when this is clearly observed no further diagnostic tests are required.[5] Some clinicians recommend that the woman lies flat or in the left lateral for a period of time before speculum examination to allow the amniotic fluid to accumulate, though no evidence was identified to support these practices. Based on clinical evaluation, the diagnosis of PPROM can be equivocal in 10–20% of cases. When a pool of amniotic fluid is not clearly observed, consideration should be given to testing for IGFBP-1 or PAMG-1 if these tests are available, and further management undertaken as per NG25.[5] Several studies investigating these biochemical markers have found high levels of sensitivity and specificity.[8,9] NG 25 emphasises that the test results for IGFBP-1 or PAMG-1 should not be used alone to decide what care to offer the woman and that clinical condition, medical and pregnancy history, and gestational age

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should be taken in to account. Testing for nitrazine is not recommended, and no further tests are required if the woman is in established labour.[5]

No studies were identified specifically addressing ultrasound to determine amniotic fluid volumes in women presenting with suspected PPROM. Ultrasound examination demonstrating oligohydramnios may be useful to support the clinical diagnosis of PPROM.

If PPROM is not confirmed, the woman can return to her previous schedule of antenatal care; NG25 recommends that women should be advised to return if they have any further symptoms suggestive of PPROM or preterm labour.[5]

Evidence level 4

It is routine practice in the UK to obtain a vaginal swab for microbiological testing while diagnosing PPROM, although evidence to support this practice is lacking. Group B streptococcus colonization may be identified, which would influence the timing of birth (section 7.1). A prospective cohort study assessed the vaginal microbiome in women following PPROM; this concluded that following PPROM the vaginal microbiome was abnormal but the profile did not correlate with latency duration.[10]

Evidence level 2+

5. Assessment

5.1 What is required antenatally to identify infection?

Recommendation	Evidence Level	Strength	Rationale for the recommendation
A *combination* of clinical assessment, maternal blood tests (C-reactive protein and white cell count) and fetal heart rate should be used to diagnose chorioamnionitis in women with PPROM; these parameters should not be used in isolation	**4**	**D**	Recommended by NG25[5]
Women should be advised of, and observed for, symptoms of clinical chorioamnionitis (lower abdominal pain, abnormal vaginal discharge, fever, malaise and reduced fetal movements)	**4**	**D**	Recommended by NG25[5]

One of the risks associated with PPROM is ascending infection leading to chorioamnionitis, and subsequent fetal and neonatal infection. NG25[5] recommends that a combination of clinical assessment (pulse, blood pressure, temperature and symptoms), maternal blood tests (C-reactive protein and white cell count) and fetal heart rate using cardiotocography, should be employed to diagnose clinical infection. If the results of the clinical assessment or any of the tests are not consistent with each other, it is recommended that the woman should continue to be observed and consideration should be given to repeating the tests as per NG25.[5]

Evidence level 4

The white cell count will rise 24 hours following administration of corticosteroids and should return to baseline 3 days following administration.[11] While a study investigating several maternal serum markers for predicting histological chorioamnionitis after PPROM concluded that a raised C-reactive protein was most informative,[12] a systematic review and meta-analysis of 13 observational studies found that

Evidence level 2++

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C-reactive protein has a sensitivity of only 68.7% and specificity of 77.1% in diagnosing histological chorioamnionitis.[13]

When cared for as an inpatient, women with PPROM should have their vital signs, including pulse, blood pressure, respiratory rate and temperature, recorded on an obstetric early warning chart.[14] They should also be observed for clinical symptoms and signs of infection. When cared for as an outpatient, women should be advised of the symptoms of chorioamnionitis and be reviewed regularly (including blood tests [white cell count and C-reactive protein], clinical recordings and fetal heart rate monitoring), for example, in a day care unit, maternity triage or antenatal ward, one or two times each week; if the woman has any concerns, she should attend the hospital immediately.

5.2 Should neonatologists be involved in the woman's care?

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Neonatologists should be informed when the diagnosis of PPROM is confirmed and delivery is anticipated	**4**	✓	It is important to ensure that the neonatal unit has the appropriate staff and facilities to care for the neonate should delivery occur
Women with PPROM should have the opportunity to meet with a neonatologist antenatally to discuss their baby's care	**4**	✓	This would be regarded as good practice

PPROM is associated with increased perinatal morbidity and mortality, and often leads to preterm birth.[1] Neonatologists should be informed once the diagnosis of PPROM has been made and delivery is anticipated to ensure that the neonatal unit has the appropriate staff and facilities to care for the neonate should delivery occur.

Where possible, once the diagnosis has been confirmed, women with PPROM and their partners should be offered the opportunity to meet with a neonatologist to discuss their baby's care.

6. Management

6.1 Should antibiotics be given?

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Erythromycin should be given for 10 days following the diagnosis of PPROM, or until the woman is in established labour (whichever is sooner)	**1++**	**A**	A Cochrane review found benefits when antibiotics were administered: reduced chorioamnionitis, prolonged latency and improved neonatal outcomes Recommended by NG 25[5]

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A Cochrane review investigating the role of antibiotics for women with confirmed PPROM found that the use of antibiotics is associated with a statistically significant reduction in chorioamnionitis (RR 0.66, 95% CI 0.46–0.96). There was a significant reduction in the numbers of babies born within 48 hours (RR 0.71, 95% CI 0.58–0.87) and 7 days (RR 0.79, 95% CI 0.71–0.89). Neonatal infection, use of surfactant, oxygen therapy and abnormal cerebral ultrasound prior to discharge from hospital was also reduced. There was no significant reduction in perinatal mortality[15] or on the health of the children at 7 years of age.[16] The antibiotic of choice and optimal duration of treatment are not clear; erythromycin 250 mg four times a day for 10 days or until the woman is in established labour (whichever is sooner), is recommended in NG25.[5] Penicillin may be used in women who cannot tolerate erythromycin. Alternative antibiotic regimens have been investigated.[17,18] Co-amoxiclav should be avoided as it is associated with an increased risk of neonatal necrotising enterocolitis,[19] and antibiotics should not be given unless the diagnosis of PPROM is confirmed.

Evidence level 1++

6.2 *What is the role of antenatal corticosteroids?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
In women who have PPROM from 24^{+0} weeks, antenatal corticosteroids should be:			Corticosteroids recommended by NG25[5] and supported by a meta-analysis of randomised controlled trials
• offered between 24^{+0} and 25^{+6} weeks of gestation	**2++**	**B**	Large cohort studies demonstrate benefits of steroids for babies born between 24^{+0} and 25^{+6} weeks of gestation
• offered between 26^{+0} and 33^{+6} weeks of gestation	**1++**	**A**	High-quality evidence that steroids reduce the incidence of intraventricular haemorrhage and the need for mechanical ventilation in PPROM
• considered between 34^{+0} and 35^{+6} weeks of gestation	**1++**	**A**	Given the high 'number to treat' and the potential side effects of steroids, administration should be evaluated on an individual basis

A meta-analysis of 17 randomised controlled trials has demonstrated that the administration of corticosteroids to women with PPROM reduces the risks of respiratory distress syndrome (RR 0.81, 95% CI 0.67–0.98) and intraventricular haemorrhage (RR 0.49, 95% CI 0.25–0.96). No difference was observed between steroid and control groups concerning the risk for necrotising enterocolitis, neonatal sepsis and Apgar score of less than 7 at 5 minutes. Perinatal mortality was similar between steroid and control groups.[20] A meta-analysis of observational studies suggest no increased risk of chorioamnionitis or neonatal sepsis with maternal steroid use.[21]

Evidence level 1++

NG25[5] addresses the administration of corticosteroids to women with PPROM from 24^{+0} until 35^{+6} weeks of gestation, recommending that when offering or considering corticosteroids a discussion should take place with the woman about how steroids may help and the potential risks associated with their administration. Furthermore, NG25 recommends that repeat courses of corticosteroids should not be routinely offered but that the interval since the last course, the gestational age and the likelihood of birth in the next 48 hours, should be taken in to account.[5]

Evidence level 4

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This Green-top Guideline covers the care of women presenting with suspected PPROM from 24^{+0} weeks' gestation. NG25[5] recommends that corticosteroids should be *considered* between 24^{+0} and 25^{+6} weeks' gestation. There is now good evidence that corticosteroid administration has benefits when given to women who give birth at less than 25^{+6} weeks' and indeed, at less than 24^{+0} weeks'.[22,23] In contrast to NG25[5] we therefore recommend that corticosteroids should be *offered* from at least 24^{+0} weeks' gestation.

Evidence level 2+

6.3 *What is the role of magnesium sulfate for neuroprotection of the baby?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
In women who have PPROM and are in established labour or having a planned preterm birth within 24 hours, intravenous magnesium sulfate should be offered between 24^{+0} and 29^{+6} weeks of gestation	**1++**	**A**	Recommended by NG25[5] and supported by meta-analyses of randomised controlled trials that have shown a reduction in cerebral palsy

Meta-analyses of randomised controlled trials have demonstrated that the administration of magnesium sulfate to women in established preterm labour or having a planned preterm birth in the following 24 hours, reduces cerebral palsy (RR 0.69, 95% CI 0.55–0.88) and motor dysfunction in the offspring (RR 0.6, 95% CI 0.43–0.83).[24–26] The benefit is greatest before 30^{+0} weeks of gestation.[25]

Evidence level 1++

The neuroprotective effect of magnesium sulfate in women with PPROM has been demonstrated in a cohort study.[27]

Evidence level 2++

The RCOG[28] and NG25[5] recommend offering magnesium sulfate to women at risk of giving birth before 30^{+0} weeks of gestation. NG25[5] recommends that magnesium sulfate should be considered when preterm birth is anticipated between 30^{+0} and 33^{+6} weeks.

Evidence level 4

6.4 *Should tocolytic agents be used?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Tocolysis in patients with PPROM is not recommended	**1++**	**A**	A Cochrane review found that tocolysis does not significantly improve perinatal outcome and might be associated with an increased risk of chorioamnionitis

A Cochrane review found that, compared with placebo, tocolysis in PPROM is associated with an average 73 hours longer latency of delivery (95% CI 20–126) and fewer births within 48 hours (RR 0.55, 95% CI 0.32–0.95).[29] Tocolysis was associated with an increased risk of a 5-minute Apgar score of less than 7 and an increased need for ventilation support. For women before 34^{+0} weeks of gestation, tocolysis increased the risk of chorioamnionitis. The review concluded that there is insufficient evidence to support the use of tocolysis in women with PPROM, as there is an increase in maternal chorioamnionitis without significant benefits to the neonate

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More recent publications have shown that compared with no tocolysis, tocolysis is not associated with improved neonatal outcomes.[30,31]

Evidence level 1+

6.5 *Can women be monitored at home?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
The decision to offer outpatient care to women with PPROM should be made on an individual basis, taking into account markers of delivery latency	**3**	✓	Retrospective cohort studies found no differences in maternal or neonatal outcomes when planned home versus hospital care was compared
The optimal method of monitoring to predict adverse fetal outcome after PPROM has not been determined	**2++**	**B**	A Cochrane review found insufficient evidence to allow recommendations

A Cochrane review to assess the safety, cost and women's views about planned home versus hospital care for women with PPROM identified only two relatively small trials (116 women) so that meaningful differences between the groups could not be detected.[32] Retrospective cohort studies from Canada (173 women),[33] and France (414 women),[34] found no difference in maternal morbidity, or neonatal morbidity or mortality between the groups

Evidence level 3

If delivery seems imminent, then in-patient care is indicated to prepare the woman for birth (including, if relevant, the administration of intravenous magnesium sulphate).

The decision to offer outpatient care to women with PPROM, following a period of in-patient care, should be made on an individual basis. Factors including past obstetric history, support at home and distance from the hospital should be taken into account in discussion with the woman about her preferences, and markers of delivery latency should be assessed (the presence of antepartum haemorrhage, amniotic fluid volume, gestational age at which PPROM occurs and clinical and laboratory markers of infection).[34,35] When considering the gestational age at which PPROM occurs, delivery latency remains relatively constant from 24^{+0} to 28^{+0} weeks' gestation at 8–10 days (median) and then decreases to 5 days (median) at 31^{+0} weeks.[3]

Evidence level 3

A case–control study has shown that women with clinically diagnosed PPROM who have reduced amniotic fluid volumes on ultrasound are more likely to give birth within 7 days from membrane rupture.[36]

Evidence level 2+

A retrospective cohort study of women with PPROM who had planned home care, found that membrane rupture occurring before 26^{+0} weeks', non-cephalic presentation and oligohydramnios were associated with an increased risk of 'complication' (defined as fetal death, placental abruption, umbilical cord prolapse, delivery outside of hospital and neonatal death). The authors concluded that hospital based care should be recommended to women who have all three of these features.[37]

Evidence level 2–

A survey of fetal medicine specialists in the United States found substantial variations in fetal monitoring following PPROM.[38] In the UK, most clinicians would monitor fetal growth on ultrasound scan fortnightly, and assess amniotic fluid and umbilical artery Doppler studies weekly, although a Cochrane review on

Evidence level 1++

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methods to monitor the fetus following PPROM found insufficient evidence (three randomised controlled trials) to allow recommendations to be made.[39]

6.6 *Is there a role for amnioinfusion in PPROM?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
In PPROM, amnioinfusion is not recommended as part of routine clinical practice	**1+**	**B**	Cochrane review found some benefits of amnioinfusion, but questioned the quality of the evidence

Amnioinfusion might improve neonatal outcomes in PPROM by preventing umbilical cord compression, postural deformities, pulmonary hypoplasia and intrauterine infection.[40] A Cochrane systematic review of five trials (using the data from four) found that amnioinfusion is associated with: improved fetal umbilical artery pH at delivery, reduced variable decelerations in labour, neonatal death, neonatal sepsis, pulmonary hypoplasia and puerperal sepsis.[40] Since the positive findings were due to one trial with unclear allocation concealment, the review authors conclude that further evidence is required before amnioinfusion for PPROM can be recommended for routine clinical practice

Evidence level 1+

A further Cochrane review investigating amnioinfusion in PPROM occurring before 26 weeks of gestation found no eligible trials.[41]

6.7 *Should women with PPROM be offered emotional support?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Women with PPROM and their partners should be offered additional emotional support during pregnancy and postnatally.	**4**	✓	Cohort studies have shown that posttraumatic stress disorder occurs in a substantial number of women whose pregnancy is complicated by PPROM.

Prospective cohort studies have shown that posttraumatic stress disorder is more common in women whose pregnancies were complicated by PPROM compared to uncomplicated controls (14% versus 2% antenatally, and 17% versus 3% at 6 weeks postnatal).[42]

Evidence level 2+

Women with PPROM and their partners should be offered access to additional emotional support, both during pregnancy and postnatally.

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7. Birth

7.1 *When is the appropriate time to deliver the baby?*

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Women whose pregnancy is complicated by PPROM after 24^{+0} weeks' gestation and who have no contraindications to continuing the pregnancy should be offered expectant management until 37^{+0} weeks; timing of birth should be discussed with each woman on an individual basis with careful consideration of patient preference and ongoing clinical assessment	1++	A	A Cochrane review found benefits from expectant management, rather than early delivery, following PPROM in women with otherwise uncomplicted pregnancies.
The care of women with PPROM who are known to be colonised with group B streptococcus, is addressed in Green-top Guideline No. 36	4	D	See RCOG Green-top Guideline No. 36.[6]

The previous edition of this Green-top Guideline recommended that delivery of the baby should be considered at 34^{+0} weeks' gestation. More recently, a Cochrane review of 3617 women explored the effect of planned early delivery versus expectant management for women with PPROM.[43] The authors conclude that in women with PPROM 'with no contraindications to continuing the pregnancy, expectant management with careful monitoring is associated with better outcomes for the mother and baby'. The Cochrane review found no differences between early birth and expectant management in neonatal sepsis or infection. Early delivery increased the incidence of respiratory distress syndrome (RR 1.26, 95% CI 1.05–1.53), and an increased rate of caesarean section (RR 1.26, 95% CI 1.11–1.44). There were no differences in overall perinatal mortality or intrauterine deaths when comparing early delivery with expectant management. Early birth was associated with a higher rate of neonatal death (RR 2.55, 95% CI 1.17–5.56) and need for ventilation (RR 1.27, 95% CI 1.02–1.58).[43]

Evidence level 1++

The results and conclusions of the Cochrane review are influenced by those trials assessing 'late' PPROM (34^{+0} to 36^{+6} weeks' gestation) such as the PPROMPT trial[2] and it is less clear whether expectant management to 37^{+0} weeks' gestation is appropriate for women who experience PPROM at earlier gestations. The Cochrane review acknowledges that research is required to determine which groups of women with PPROM would not benefit from expectant management, including gestational age at presentation.

The individual studies included in the Cochrane review[43] had a number of 'exclusion criteria' including: active labour, chorioamnionitis, concerns about fetal wellbeing, monochorionic multiple pregnancy, hypertensive disorders and other contraindications to continuing the pregnancy. Therefore the timing of birth should be discussed with each woman on an individual basis with careful consideration of patient preference and ongoing clinical assessment.

RCOG Green-top Guideline No. 36[6] addresses the management of PPROM in women known to be colonized with group B streptococcus

Evidence level 4

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8. Care in a subsequent pregnancy following PPROM

8.1 *Who should care for woman in a subsequent pregnancy?*

Recommendation	Evidence Quality	Strength	Rationale for the recommendation
In a subsequent pregnancy following PPROM, women should be cared for by an obstetrician with an interest in preterm birth	**4**	✓	The risk of PPROM in subsequent pregnancies is increased

A population based cohort study found that pregnancies complicated by PPROM are at increased risk of recurrent PPROM in subsequent pregnancies (OR 8.7, 95% CI 6.7–11.4 in white women and OR 7.2, 95% CI 5.1–10.1 in African American women).[44] This study also found that a short inter-pregnancy interval is associated with greater risk

Evidence level 2+

In pregnancies following PPROM, women should be cared for by an obstetrician with an interest in preterm birth; ideally this would be in a dedicated preterm labour clinic. Modifiable risk factors, such as smoking[45] and respiratory diseases[46] should be addressed. There is evidence that screening for lower genital tract infections and midwife continuity throughout antenatal care are beneficial in preventing preterm birth.[47] Clinicians may offer these women genital tract screening for infection and/or serial transvaginal ultrasound scans to determine the cervical length, but the evidence to support these interventions is lacking.[5]

9. Recommendations for future research

- Studies are required to determine the antibiotic of choice and duration of treatment following PPROM.
- Controlled trials are required to determine whether magnesium sulphate has a role in PPROM when delivery is anticipated between 30^{+0} and 33^{+6} weeks of gestation.
- Studies comparing a single bolus of magnesium sulphate with a longer intravenous infusion are required.
- Methods to monitor the fetus following PPROM require further investigation.
- The role of sealants to 'repair' fetal membranes is currently under investigation.
- Studies are required to determine whether there is a role for amnioinfusion in PPROM.
- Trials are needed to determine which groups of women with PPROM would not benefit from expectant management.

10. Auditable topics

- Proportion of women with PPROM who are offered antibiotics for 10 days following PPROM, or until the woman is in established labour (100%).
- Proportion of women who experience PPROM between 24^{+0} and 33^{+6} weeks of gestation who are offered corticosteroids (100%).
- Proportion of women less than 30^{+0} weeks' gestation who receive magnesium sulphate within 24 hours prior to birth (100%).
- Proportion of women with PPROM who are given the opportunity to discuss their care with a neonatologist (100%).
- Proportion of women with PPROM who birth in a centre without adequate facilities to care for their baby (0%)

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11. Useful links and support groups

- Royal College of Obstetricians and Gynaecologists. *When your waters break early*. Information for you. London: RCOG; 2019.
- Little Heartbeats, a support group that promotes the awareness of PPROM [www.little-heartbeats.org.uk].

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Infographic S1. Infographic version of the guideline

Audio S1. Audio version of the guideline

Appendix S1. PPROM literature search strategy

Appendix S2. PPROM search strategy top up

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The guideline will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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