BJOG: An International Journal of Obstetrics & Gynaecology

WILEY

BJOG An International Journal of Obstetrics and Gynaecology

RCOG SCIENTIFIC IMPACT PAPER

Care of Women With Preterm Prelabour Rupture of the Membranes Prior to 24^{+0} Weeks of Gestation

Scientific Impact Paper No. 76

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Funding: All those involved in the development of Scientific Impact Papers, including the Scientific Advisory Committee, Scientific Advisory Committee chair, developers, peer reviewers and other reviewers, are unpaid volunteers and receive no direct funding for their work in producing the paper. The only exceptions to this are the Scientific Advisory Committee members who receive reimbursement for expenses for attending Scientific Advisory Committee meetings for standard RCOG activities; this is standard as per RCOG rules.

Plain Language Summary

Rupture of the membranes is commonly referred to as 'waters breaking'. This usually occurs just before or during labour. In around three in 100 pregnancies it occurs before 37^{+0} weeks of pregnancy (preterm), but the woman does not go into labour within 24 h: this is called preterm prelabour rupture of the membranes (PPROM). These women often give birth preterm. This paper looks at PPROM before 24^{+0} weeks of pregnancy. This happens in a much smaller number of women.

PPROM prior to 24^{+0} weeks of pregnancy is particularly concerning because of the chance of the baby being born extremely preterm. It is considered in the best interest of the baby not to offer resuscitation and intensive care if they are born before 22^{+0} weeks, meaning that these babies do not survive. Babies born between 22^{+0} and 26^{+0} weeks are at risk of severe and sometimes life-long problems. They also have a lower chance of survival than babies born later. Women sometimes develop an infection after PPROM, which can be extremely dangerous. If this happens, doctors will discuss ending the pregnancy even if the baby is very unlikely survive so that the woman does not become unwell (termination for a medical reason). However, some babies do survive and are discharged home, well, and most mothers have no long-term physical problems.

This situation is very difficult for women who are pregnant, as well as their partners and wider families. It is made more difficult by a lack of clear information for doctors and midwives about how well women and babies in this situation will do, and how to look after them. This can result in lots of variation in information and care for women.

Here we summarise the current evidence about this condition. Firstly, we explain available information on how well women and babies are likely to do. Then we discuss evidence about predicting the problems individual women and babies might have. Finally, we look at evidence on the ways in which healthcare professionals can care for women and their babies up to birth.

1 | Introduction

Preterm prelabour rupture of the membranes (PPROM) occurs when the fetal membranes rupture prior to 37^{+0} weeks of gestation and is associated with a variety of adverse maternal and fetal outcomes. Risk of mortality and severe morbidity is inversely associated with gestational age at membrane rupture. While there is a growing body of evidence on management of PPROM at or after 24^{+0} weeks of gestation, which has resulted in recent comprehensive clinical guidance [1, 2], there is a paucity of evidence

This is the first edition of this paper.

and guidance regarding optimal management of PPROM prior to this. PPROM at less than 24^{+0} weeks of gestation occurs in at least 1 in 2750 pregnancies and represents a group at particularly high risk of maternal and perinatal morbidity and mortality [3, 4]. In addition to the complexities surrounding management of pregnancies at risk of imminent birth at the extremes of gestational age and birthweight [5], PPROM at this gestation may be a clinical indication for termination of pregnancy for medical reasons (TFMR) [2]. Uncertainty surrounding clinical outcomes as well as complex management decisions also leaves women at high risk of psychological morbidity [6–8]. Taken together, this represents a complex situation as regards counselling of women and their families in order to facilitate their decision making. There is no national guidance on this condition, and women who have experienced it describe significant variations in counselling and practice [8]. Regarding language used in this guidance, previable birth has a variable definition internationally, but is taken to mean birth prior to 22^{+0} weeks' gestation. The evidence in this paper relates to spontaneous PPROM; while there is likely to be significant overlap with iatrogenic PPROM, professionals should be wary of applying the information stated here to this different clinical scenario.

The purpose of this Scientific Impact Paper is to advise on emerging evidence on the outcomes and management of PPROM at less than 24^{+0} weeks of gestation, and its implications for practice and future research. This is achieved via review of published literature from the past 20 years (although older literature is referred to where no more up-to-date evidence is available) and international guidance, and with collaboration from relevant patient groups.

This guidance is for healthcare professionals who care for women, non-binary and trans people who experience PPROM. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2 | Outcomes of Pregnancies Following PPROM <24^{+0} Weeks of Gestation

Counselling of women with PPROM and their families is critical to facilitate informed decision making. Historical concerns about invariably poor fetal and neonatal outcomes are changing as neonatal care advances, and women should be counselled based on individual risk, including gestation at membrane rupture. Nonetheless, the risk of maternal deterioration, fetal demise, previable birth, or birth at the extremes of viability with the associated risks of neonatal death or long-term neurodisability, renders counselling complex—particularly concerning decisions for TFMR versus expectant management.

All research on PPROM is limited by diagnostic techniques used. The gold standard remains visualisation of amniotic fluid in the posterior fornix [1]. Given the smaller volume of amniotic fluid at lower gestations, it is possible this would be harder to identify prior to 24^{+0} weeks. It has become clinical practice to use any of a number of commercially available bedside immunochromatographic tests when the diagnosis is uncertain [9]. However, evidence for these tests is lacking, with initial investigation often undertaken against now discredited tests, such as fern or nitrazine testing. Even taking this into account, false positive rates of up to 9% have been suggested (likely an underestimation given the validation techniques described above) [10]. Furthermore, study conditions where women have 'signs and symptoms' are not replicated in clinical practice where tests are used in equivocal cases (where women tend to have symptoms but not signs) [11]. Ultrasound is not recommended in isolation as a diagnostic tool for PPROM owing to a lack of sensitivity; where oligohydramnios is noted and the diagnosis of PPROM is equivocal, then fetal medicine specialist review would be warranted to rule out other causes of anhydramnios, such as a severe renal anomaly. As well as potentially poor diagnostic accuracy being a consideration when reviewing research, improved diagnostic techniques is an essential aspect of research going forward as well as a limitation of our clinical abilities that women should be made aware of during counselling.

2.1 | Maternal Outcomes

The UK Obstetric Surveillance System (UKOSS) study on Preterm Prelabour Rupture of the Membranes prior to 23^{+0} weeks of gestation prospectively collected data nationally from women with pregnancies complicated by PPROM prior to 23^{+0} weeks of gestation between 1 September 2019 and 28 February 2021 (a subgroup analysis was undertaken to consider the impact of the Covid-19 pandemic and no statistically significant difference was seen, so the entire dataset is considered here). This demonstrated a 10% maternal sepsis rate among women who had TFMR, compared to 13% among women who initially had expectant management. The maternal mortality rate reported was 0.5% (~55/10000 women, both secondary to sepsis) [4], although a 15-year analysis of the French Confidential Enquiries into Maternal Deaths gave a more conservative estimate with a previable PPROM attributable maternal mortality rate of 0.6/10000, and a mortality rate among women with previable PPROM of 4.5/10000 (95% CI 1.4–9.2) (previable defined as 14^{+0} to 24^{+6} gestational weeks) [12]. Whether PPROM occurs secondary to chorioamnionitis, or chorioamnionitis occurs secondary to the loss of the maternal-fetal barrier after PPROM is unclear and likely dependent on underlying pathology; in any case, genital tract sepsis remains a common cause of death [4, 13]. In the UK Confidential Enquiries into Maternal Deaths, the 2019–2021 report highlighted that two (of a total of 241 maternal deaths in the triennia) occurred following sepsis directly attributable to second trimester PPROM [13].

A retrospective study from three institutions in the USA studied 208 women in three US institutions who experienced PPROM before 24^{+0} weeks of gestation between 2011–2018 and who either had expectant management (51.9%) or TFMR (48.1%). Compared to women who had TFMR, women who had expectant management had 4.1 times increased risk of developing chorioamnionitis (38.0% vs. 13.0%; 95% confidence interval,

2.03–8.26, $p < 0.001$) and 2.44 times the odds of postpartum haemorrhage (23.1% vs. 11.0%; 95% confidence interval, 1.13–5.26, $p = 0.027$). Admissions to the intensive care unit and unplanned hysterectomy only occurred after expectant management (2.8% vs. 0.0 and 0.9% vs. 0.0 respectively). Of women who chose expectant management, 36.2% gave birth via caesarean section with 56.4% not having a low transverse incision to the uterus. Composite maternal morbidity rates (encompassing chorioamnionitis, unplanned surgery, unplanned hysterectomy, blood product transfusion and intensive care unit admission) were 60.2% in the expectant management group and 33.0% in the TFMR group ($p < 0.001$). After adjusting for gestational age at PPROM, site, race and ethnicity, gestational age at entry to prenatal care, PPROM in a previous pregnancy, twin pregnancy, smoking, cervical cerclage, and cervical examination at the time of presentation, expectant management was associated with 3.47 times increased risk of composite maternal morbidity (95% confidence interval, 1.52–7.93), corresponding to an adjusted relative risk of 1.91 (95% confidence interval, 1.35–2.73). Among women who chose expectant management, 15.7% avoided morbidity and had a neonate who survived to discharge [14]. While this study did not comment on the need for manual removal of placenta specifically, the UKOSS study also highlighted a 20% rate among all women with PPROM prior to 23^{+0} weeks of gestation regardless of gestational age at birth, which is in line with previous reports [3].

2.2 | Fetal and Neonatal Outcomes

Major risks to the survival of a fetus and neonate following PPROM include previable birth, complications of extreme prematurity, pulmonary hypoplasia, overwhelming sepsis, and other PPROM-associated complications such as cord prolapse or placental abruption. While the British Association of Perinatal Medicine (BAPM) framework provides useful data on neonatal survival for counselling parents when birth is imminent at extremes of gestational ages, it does not mention PPROM or chorioamnionitis as non-modifiable risk factors that should be used to adjust the risk of a poor outcome [5], thereby limiting its usefulness in this group. Women who experience PROM earlier in the midtrimester have a higher chance of birth before viability (Table 1), a factor that must be considered in counselling, both in terms of risk of second trimester pregnancy loss but also when considering best place of care (i.e., whether admission and/or transfer of care and planning for birth in a tertiary unit is most appropriate). Data described in Table 1 includes all expectantly managed cases and it must be noted that there was a 56% intrauterine death or previable birth rate in this group, including a 16% intrauterine death rate among cases delivered from 22^{+-0} weeks of gestation onwards.

The UKOSS study findings highlighted that 31% of women chose to end the pregnancy (with the highest rate of termination seen in women who had PPROM at under 18^{+0} weeks of gestation) and 69% chose to continue with the pregnancy. Of women continuing with a singleton pregnancy, 44% (98/223) had a liveborn child, and 18% (38/207) had a child that survived to hospital discharge without severe morbidity. Severe morbidity was defined as grade 3 or 4 intraventricular haemorrhage and/or requirement for oxygen at 36 weeks postmenstrual age (the commonly used definition of bronchopulmonary dysplasia). The range of worst-best outcomes if women who had a TFMR were included within the analysis as if they had an ongoing pregnancy are a livebirth rate of 30–62% and a child survival to discharge without severe morbidity of 12–48%. There was no significant difference between morbidity outcomes surviving babies at earlier versus later gestation at PPROM (Table 2), although there was a trend towards higher rates of survival to discharge without severe morbidity if PPROM occurred from 20^{+0} weeks of gestation. Longer term outcomes are not available.

An older retrospective single-centre study from The Republic of Ireland identified 42 women with PPROM before 24^{+0} weeks of gestation between 2007 and 2012 (when termination was not possible unless the woman's life was in danger) indicated a livebirth rate of 24% but with only 5% of infants surviving to discharge [3]. Mean gestation at membrane rupture was 18^{+0} weeks and birth 20^{+5} weeks of gestation, as compared to 19^{+3} and 22^{+4} weeks of gestation (for women not having TFMR) respectively in the UKOSS study, which provides some explanation for the discrepancy in infant survival data. Although it is equally plausible that this difference is at least partially attributable to improved neonatal care over time for extremely preterm babies. There is a growing body of evidence looking at neonatal outcomes of survivors. The EPIPAGE-2 study conducted a secondary analysis of outcomes in PPROM from 22^{+0}–25^{+0} weeks of gestation and demonstrated a 10.5% and 36.0% survival to 2 years without cerebral palsy in babies where PPROM had occurred at 22^{+0} and 23^{+0} weeks of gestation respectively [15]. Another retrospective

TABLE 1 | Latency to birth by gestational age at preterm prelabour rupture of the membranes following decision for expectant management (data from the UKOSS study, including spontaneous onset and induction of labour, but excluding termination of pregnancy) [4].

	Gestational weeks at preterm prelabour rupture of the membranes, *n* (%)			
	16^{+0}–17^{+6}	18^{+0} – 19^{+6}	20^{+0}–21^{+6}	22^{+0}–22^{+6}
Latency to birth	***n* = 43**	***n* = 70**	***n* = 80**	***n* = 30**
<72 h	16 (37)	18 (26)	20 (25)	6 (20)
72 h to <7 days	27 (9)	8 (11)	9 (11)	6 (20)
7 days to <28 days	6 (14)	12 (17)	24 (30)	6 (20)
≥28 days	17 (40)	32 (46)	26 (33)	10 (33)
Unspecified	0	0	1 (1)	2 (7)

TABLE 2 | Neonatal outcome following preterm prelabour rupture of the membranes. (Data from the UKOSS study) [4]. Severe morbidity is defined as: Grade 3–4 intraventricular haemorrhage or supplemental oxygen requirement at or beyond 36 weeks' postmenstrual age in singleton pregnancies.

	Gestational weeks at preterm prelabour rupture of the membranes, *n* (%)			
	16^{+0}–17^{+6}	18^{+0}–19^{+6}	20^{+0}–21^{+6}	22^{+0}–22^{+6}
Outcome	***n* = 82**	***n* = 102**	***n* = 105**	***n* = 37**
Livebirth	14 (17)	27 (26)	37 (35)	20 (54)
Survival to discharge	*7*	*16*	*21*	*10*
Discharge without severe morbidity	*5*	*11*	*13*	*10*
Neonatal Death	*4*	*8*	*10*	*6*
Livebirth with unknown discharge status	*3*	*3*	*6*	*4*
Termination for medical reasons	39 (48)	32 (31)	25 (24)	7 (19)
Birth or intrauterine death <22 + 0 weeks of gestation	26 (32)	37 (36)	27 (26)	n/a
Intrauterine death >22 + 0 weeks of gestation	3 (4)	6 (6)	16 (15)	10 (27)

study (that excluded women undergoing termination of pregnancy) gives a 49% survival rate to discharge among neonates following PPROM at 20^{+0}–24^{+0} weeks of gestation, with 47% of survivors experiencing severe neonatal morbidity; the mortality rate after discharge from neonatal care was not recorded [16]. One study compared outcomes of early (<25^{+0} weeks) and later (25^{+0}–31^{+0} week) PPROM demonstrating a significantly higher rate of severe morbidity (51.5 vs. 22.5%; defined as moderate to severe cerebral palsy or a Bayley II score more than two standard deviations below the mean) among survivors in the early PPROM group [17]. However, these neurological differences may represent the impact of chorioamnionitis on the preterm brain, rather than the impact of PPROM alone, with significantly increased rates of per- and intraventricular haemorrhage, intracerebral haemorrhage and neonatal seizures demonstrated in a study of 9633 neonates born prior to 34^{+0} weeks of gestation with chorioamnionitis as compared to those without [18].

2.3 | Prediction of Outcomes

2.3.1 | Prediction of Pulmonary Hypoplasia

Amniotic fluid is vital in antenatal lung development, both in terms of achieving normal volume and production of important mediators of subsequent pulmonary function such as surfactant. Pulmonary hypoplasia, defined as a reduction in lung cells, airway, alveoli resulting in reduced organ size, but practically almost always used to refer to a reduction in alveoli, can occur secondary to PPROM with incidence increasing with decreasing gestational age [19]. Given that formal diagnosis requires postmortem assessment, postnatal identification is also challenging and largely based on secondary complications such as pulmonary hypertension or high oxygen requirements [20]. One systematic review of outcomes following PPROM prior to 24^{+0} weeks of gestation identified one study that looked specifically at survival of babies with clinical pulmonary hypoplasia, quoting a 64% mortality rate in affected liveborn infants (mean latency to birth 20–43 days). Although they note that this figure may under-represent true mortality as babies who died in the first 24 h of life were less likely to have a clinical diagnosis prior to death [21].

Amniotic fluid assessment has been investigated to determine risk of pulmonary hypoplasia. A prospective study of 580 women with PPROM between 20^{+0} and 28^{+0} weeks of gestation has demonstrated that a single deepest vertical pool (SDVP) of < 2 cm at presentation is associated with worse respiratory outcomes [22]. A smaller study of 31 women with PPROM <24 + 0 weeks' gestation has suggested reduced neonatal survival where the SDVP is < 1 cm [23]. Both studies suggest that a higher SDVP increases latency to birth, which could explain the improvement of respiratory and survival outcomes independent of the SDVP.

Two-dimensional ultrasound measures, such as the thoracic circumference, lung to head ratio [24] and quantitative lung index (= lung area/(head circumference/10)) [2] have been evaluated as prognostic markers for pulmonary hypoplasia and poor outcome in foetuses with congenital diaphragmatic hernia [25, 26]. However, these techniques are not validated in women with second trimester PPROM, and many studies are limited by verification bias of diagnosis of membrane rupture; therefore, these techniques have limited prognostic accuracy [27]. Three-dimensional ultrasound using virtual organ computer-aided analysis, has been demonstrated to have good prediction of lung volumes in pulmonary hypoplasia as compared to postmortem volumes. However, it is technically challenging, and is severely limited by fetal position and acoustic shadow, including from a lack of amniotic fluid, so is not clinically useful. While multiplanar 3D ultrasound is less technically challenging, its results have not been shown to predict neonatal outcome [28]. Although magnetic resonance imaging (MRI) is not validated for pulmonary hypoplasia prediction it may carry value in overcoming sonographic challenges associated with anhydramnios; one small study has demonstrated that volumetry can be used to predict

neonatal mortality secondary to respiratory distress following PPROM between 16^{+0} and 27^{+0} weeks of gestation [29]. A larger trial using MRI to predict pulmonary hypoplasia is underway. Despite progress in other congenital pulmonary conditions, the difficulty in prediction of pulmonary hypoplasia in PPROM limits its individual counselling and neonatal planning.

2.3.2 | Prediction of Arthrogryposis

Arthrogryposis, multiple congenital limb contractures, is a condition with heterogenous aetiology sometimes associated with PPROM at $<24^{+0}$ weeks of gestation owing to reduced potential for fetal movements [30]. The prevalence of arthrogryposis associated with PPROM is not well documented: the UKOSS study reports two cases of 54 surviving babies with one or two limbs affected [4]; a retrospective study of 130 neonates born following PPROM prior to 24^{+0} weeks of gestation describes a 29% rate of limb contractures [16]; larger studies of the aetiology of arthrogryposis demonstrate a much lower incidence suggesting the prevalence of arthrogryposis 1/3000 overall, with only around 1% of these cases associated with any cause of oligohydramnios [31].

The rarity of arthrogryposis and its diverse aetiology results in available evidence being difficult to interpret in the context of PPROM. Prediction of arthrogryposis is challenging, with around 75% of cases not diagnosed in the antenatal period (all aetiologies) [32]. Arthrogryposis in the context of PPROM is likely to be even more difficult to diagnose owing to poorer quality imaging in the presence of oligohydramnios, and an absence of other syndromic findings pointing towards a diagnosis. Treatment is widely varied; arthrogryposis secondary to oligohydramnios is normally responsive to physical therapies [31], whereas syndromic causes are more commonly associated with a need for surgeries [33].

2.3.3 | Prediction of Maternal and Fetal Infection

While expediting birth in cases of clinical chorioamnionitis is essential in providing safe obstetric care, reliable antenatal diagnosis of infection remains elusive. Current practice of monitoring maternal symptoms, white cell count (WCC) and C-reactive protein (CRP) are of limited value across all gestations. While maternal pyrexia is sensitive (94–100%) at temperatures at and above 38°C, it is non-specific in the absence of other symptoms, most of which are relatively insensitive (e.g., maternal tachycardia 50–70% sensitive; foul-smelling discharge 5–22% sensitive) [34]. While there may be some concern regarding method of monitoring temperature, studies in adults have demonstrated axillary assessment with a digital thermometer most reliable, excluding the significantly more time-consuming 12-min gallium in glass test, which was most reliable overall [35]. Significantly, there are inconsistencies throughout the literature on the definition of a pyrexia, with a range from 37.5–38.3°C reported by studies, which hampers interpretation of predictive value, with some also including temperatures of below 36°C within their analysis [34, 36–38]; therefore, it is noteworthy that current UK guidance on determining the presence of clinical chorioamnionitis in PPROM does not define a threshold for pyrexia [1, 9].

Likewise, WCC is relatively sensitive in the presence of corroborating symptoms, but not useful without them; CRP has not been demonstrated to be of value [34]. There has been some interest in the neutrophil to lymphocyte ratio as a marker of chorioamnionitis in clinically well women, but this has not been studied specifically in the context of PPROM at any gestation, nor have there been attempts to analyse the impact of integration into clinical practice [39]. No study has examined these parameters in early gestations specifically, although there is no reason to think they would be more reliable. While there is evidence that an increase in fetal heart rate of greater than 10% from baseline is associated with term chorioamnionitis [40], this has not been replicated in the preterm group. Fetal tachycardia is likely to be less sensitive at early gestations owing to the physiological effects of unopposed sympathetic activity [41].

Multiple studies have examined the intra-amniotic environment via either amniocentesis or transvaginal collection of amniotic fluid following PPROM. Studies including women with PPROM prior to 24^{+0} weeks of gestation have suggested diagnostic utility of multiple markers including, but not limited to, interluekin-8 [42], matrix metalloproteinase-8 [43], monocyte chemoattractant protein-1 [42] and tumour necrosis factor-α [44]. In particular, interleukin-6 has been investigated, including on bedside immunochromatography, but not prior to 24^{+0} weeks of gestation [44–47]. However, there is a paucity of large-scale clinical trials, and so no significant translation into clinical practice.

Fetal imaging to diagnose fetal inflammatory response is also an active area of research [48]. There have been multiple attempts to determine the value of ultrasound Dopplers in predicting a clinical diagnosis of chorioamnionitis: a retrospective study of 504 women with PPROM from 23^{+0} to 34^{+0} weeks of gestation compared those with and without suspected chorioamnionitis and confirmed no difference in umbilical or middle cerebral artery pulsatility index, with a poor predictive value in both tests (area under the curve [AUC] 0.619, 95% CI 0.424–0.813 and AUC 0.442, 95% CI 0.265–0.618 respectively) [49]. To our knowledge, no work undertaken at earlier gestational ages is available.

A meta-analysis of 12 studies of 1744 participants found that chorioamnionitis is more common when ultrasound assessed thymic size is decreased (73.9% of cases compared to 27.1%), although none of the studies included pregnancies at less than 24^{+0} weeks of gestation [50]. While small studies have attempted to utilise assessment of adrenal glands to predict preterm birth, none have specifically attempted to determine the impact of chorioamnionitis [48]. Studies are ongoing looking at the utility of MRI given promising differences in predicting birth in women at high risk of birth prior to 32^{+0}weeks of gestation [51–53].

Complementary to ongoing clinical studies are recent developments in animal models to aid understanding of pathophysiology of chorioamnionitis with and without PPROM. Extensive ovine work investigating the impact of lipopolysaccharide (LPS) induced chorioamnionitis on individual fetal organs is likely to inform decisions on imaging targets [54–57]. Furthermore, significant steps have been made to address the longstanding concern regarding whether LPS can truly replicate clinical infection by development of a murine model of intravaginal

E. coli infection [58]. Ongoing close working between the basic and clinical sciences remains key in improving knowledge and outcomes.

3 | Antenatal Management of Pregnancies Affected by PPROM <24 Weeks^{+0} of Gestation

3.1 | Place of Care

One study has evaluated risks of outpatient management in women with PPROM at any gestation. Women with PPROM prior to 26^{+0} weeks of gestation were found to have a significantly increased risk of complications (fetal or neonatal death, placental abruption, umbilical cord prolapse or birth outside of a maternity unit) if managed as an outpatient (odds ratio [OR] 6.2, 95% confidence interval [CI] 1.6–23.8) [59]. Although this does not negate the role of outpatient management, women should be considered high risk and there should be a very low threshold for admission. Where there are clinical concerns about evolving sepsis or impending abruption, women must remain as inpatients. When a decision has been made for consideration of neonatal resuscitation at birth, women should be cared for by an experienced multidisciplinary team in a unit with suitable neonatal facilities; in complex cases assessment by a fetal medicine specialist and a senior neonatologist would allow for site-specific decision making.

3.2 | Antibiotic Use

Optimal gestation to commence a course of prophylactic oral antibiotics is unclear, as is choice of antibiotic and duration of course. Rationale for administration after 24^{+0} weeks of gestation is from a Cochrane review that demonstrates increased latency to birth and reduction in short-term neonatal complications, without impact on maternal or neonatal mortality, or long-term infant outcomes when antibiotics are given [60]. However, this review is all gestations, and there are no subgroup analyses by gestational age at PPROM; the number of women with PPROM prior to 24^{+0} weeks of gestation who are included is unclear.

The largest study to date of oral antibiotic use in PPROM recruited 4826 women into a randomised placebo-controlled trial. While there was no lower gestational age for inclusion, there was no subgroup analysis for very early gestations. Administration of erythromycin rather than placebo was associated with a significantly increased delay to birth of 48 h, as well as a reduction in composite neonatal morbidity [61, 62].

3.3 | Antenatal Corticosteroid and Magnesium Sulphate Use

Evidence for the use of antenatal corticosteroids (ACS) prior to 24^{+0} weeks of gestation is lacking. One observational study carried out over 15 years demonstrated a reduction in death or neurodevelopmental delay in babies born at 23^{+0} weeks of gestation or later (68.4% versus 90.5%); the same was not true of babies born at 22^{+0} weeks of gestation [63]. There is no higher quality evidence than this. BAPM does not support universal use prior to 24^{+0} weeks of gestation [5].

There is increasing evidence that administration of antenatal steroids close to time of birth confers greatest risk reduction; therefore, ACS should ideally not be given more than seven days prior to birth, and repeated doses avoided as they are associated with reduction in birthweight and may worsen neurodevelopmental outcomes. Given the higher rate of pulmonary hypoplasia in neonates born following PPROM at under 24^{+0} weeks of gestation, appropriate timing of steroids is of even more importance. There has been some concern regarding the administration of steroids to women at high risk of infection. While the ACT trial, which was performed in seven low- and middle-income countries, did show a trend towards increased rates of chorioamnionitis among women who received ACS (OR 1.46, 95% CI 0.81–2.66) [64], this has not been replicated in the most recent Cochrane review, which included 15 RCTs, including the ACT trial (OR 0.86, 95% CI 0.69–1.08) [65].

There is no evidence for the use of magnesium sulphate prior to 24^{+0} weeks of gestation, although it would be pragmatic to consider this if steroids have been given and there is a plan for neonatal resuscitation.

3.4 | Tocolysis

The role of tocolysis in PPROM at any gestation is uncertain as best evidence fails to demonstrate neonatal benefit, and suggests a potential increase in the incidence of 5 min Apgar scores of <7 and invasive ventilation use, while demonstrating an increased rate of chorioamnionitis when given in cases of PPROM prior to 34^{+0} weeks of gestation. No subgroup analysis was performed where membrane rupture occurred prior to 24^{+0} weeks of gestation [66]. While the EPIPAGE-2 study does include women with PPROM between 22^{+0} and 25^{+0} weeks of gestation some of whom had received tocolysis [15], no subgroup analysis of outcomes is available [67]. Given that current advice in the UK is to not give tocolysis to women with PPROM after 24^{+0} weeks of gestation [1], it is unlikely that the recent UKOSS study of PPROM prior to 23^{+0} weeks will add granularity here [4]. However, the TOCOPROM trial (currently recruiting in France) is investigating the role of tocolysis in women with PPROM between 22^{+0} and 33^{+0} weeks of gestation in women with singleton pregnancies (nifedipine versus placebo in a randomised, double-blinded superiority trial). Although, numbers of women included prior to 24^{+0} weeks of gestation are likely to be small (the total recruitment aim for the trial is 850 women) this may provide further evidence on management of women with PPROM prior to 24^{+0} weeks of gestation [68].

3.5 | Bedrest

There is no evidence supporting the use of bedrest to improve outcomes of PPROM at any gestation: a pilot randomised control trial of 32 women with PPROM from 24^{+0} weeks of gestation demonstrated no maternal or neonatal benefit [69]. A single-centre study over a two-year period found a significantly increased risk of venous thromboembolism (VTE) in women

advised three or more days of bedrest as part of the management of PPROM as compared to the background population (15.6 cases per 1000 births, and 0.8 per 1000 births respectively) without any obstetric benefit [70]. However, it should be noted that national recommendations for VTE prophylaxis at the time of this study, would have resulted in no women being given low molecular weight heparin (LMWH) [71]. Nonetheless, current guidance would not insist on LMWH [72] and decision making surrounding prescription is complicated by risk of labour, meaning that these results continue to have validity even if awareness around the risk of VTE is greater now.

3.6 | Management of Pregnancies With Cerclage in Situ

Absolute indications for the removal of a cervical cerclage are no different in women prior to 24^{+0} weeks of gestation and include: confirmed labour, ongoing antepartum haemorrhage, maternal sepsis, fetal demise, and decision for imminent vaginal birth [73].

The best course of action for management of cerclage in women with PPROM prior to 24^{+0} weeks of gestation and no absolute indication for delivery is uncertain. Existing evidence is limited in its application given higher gestational ages at membrane rupture and variable antibiotic protocols. A recent systematic review and meta-analysis of cerclage removal versus retention at all preterm gestations following PPROM demonstrated a decreased risk of delivery within 48 h in the retention group (OR 0.15, 95% CI 0.07–0.31), but decreased rates of chorioamnionitis and 1 min Apgar <7 in the removal group (OR 0.57, 95% CI 0.34–0.96 and OR 0.22, 95% CI 0.08–0.56 respectively) [74]. Another review of multiple studies proposed that cerclage retention is associated with increased rates of maternal pyrexia and chorioamnionitis without improved latency [75]. However, in all cases antibiotic use was not consistent between studies, and poor outcomes seem to be associated with no antibiotic use, especially given the apparent better outcomes in more recent work (where antibiotic protocols are in place) [76]. One study evaluated impact of cerclage retention or removal across gestations, and demonstrated a significantly increased risk of chorioamnionitis in the cerclage retention group if PPROM occurred prior to 28^{+0} weeks of gestation [77]. No group has demonstrated neonatal benefit following cerclage retention or removal at time of PPROM.

3.7 | Investigation and Management of Group B Streptococcus

Current RCOG guidance on the management of group B streptococcus (GBS) in pregnancy does not recommend GBS testing after PPROM [78]. This is a pragmatic recommendation as current NICE guidance for intrapartum GBS prophylaxis is risk-based and all cases of preterm labour or women with ruptured membranes for >24 h would receive intrapartum antibiotics regardless of GBS status on swab [9]. Furthermore, current methods for GBS testing (low vaginal and anorectal swab) are not validated in PPROM. Evidence for whether routine testing for GBS in women with PPROM impacts outcome is lacking at all gestations.

3.8 | Termination of Pregnancy

The most recent UK data demonstrates that 31% of women with PPROM prior to 23^{+0} weeks of gestation underwent termination, with this being more common when PPROM occurs at earlier gestations [4]. Grounds for termination include risk to maternal health (risks of expectant management versus TFMR are discussed in 2.1), and concerns about perinatal morbidity and mortality (see section 2.3.1). In cases where TFMR is not because of risk to the woman's life, current RCOG advice on the use of feticide prior to termination should be followed (generally, to be offered where termination is to occur after 21^{+6} weeks of gestation). Where feticide is not being performed prior to TFMR, women should be advised of the risk of signs of life following birth based on their gestation [79]. It should be noted by healthcare providers that in cases where maternal health is at risk rapid delivery via dilatation and evacuation may be the safest way to deliver a baby [80].

3.9 | Amnioinfusion and Amniopatching

A Cochrane review evaluating amnioinfusion in the 3rd trimester for women with PPROM was undertaken in 2014, finding sparse data and lack of methodological robustness [81]. The AMNIPROM pilot study demonstrated feasibility of amnioinfusion studies, but highlighted longer term neonatal outcomes as necessary endpoints [82]. Trials are currently underway in Germany for the management of 2nd trimester PPROM with amnioinfusion [83].

Amniopatching was considered in a 2016 Cochrane review. Two studies, both deemed at high risk of bias, were included and there was considered to be inadequate evidence for recommendation in clinical practice [84]. In any circumstance, neither procedure should be offered outside of a clinical trial.

3.10 | Emotional Support

Women with PPROM are at higher risk of antenatal anxiety, postnatal depression and post-traumatic stress disorder [6, 7, 85]. In this setting, best therapies and management of psychological morbidity are not known despite the significant additional burden placed on women by these comorbidities. Furthermore, there is very limited evidence of the impact of PPROM and its complications on the partners of affected women. Women themselves describe well-informed medical teams, comprehensive information and compassionate care as necessary for improving their own feeling of psychological wellbeing, as well as more formal psychological support [8].

3.11 | Multiple Pregnancies

Evidence of optimum management of and outcomes related to second trimester PPROM in multiple pregnancies is lacking. Data from the UKOSS study (23 dichorionic diamniotic (DCDA) twins and 10 monochorionic diamniotic (MCDA) twins) demonstrated a 20% survival to discharge rate for both twins, with single twin survival in a further 17% of pregnancies. However, management was complicated in six cases by either single twin

birth or intrauterine demise prior to 22^{+0} weeks of gestation, highlighting the complexity in management of such pregnancies [4]. There is no evidence on relative outcomes when there is single twin PPROM with preserved amniotic fluid in the second twin.

4 | Intrapartum Management

4.1 | Optimum Timing of Birth

There is histopathological evidence from a single-centre that delaying birth until 34^{+0} weeks of gestation in women with known genital tract GBS colonisation who have PPROM from 23^{+0} weeks of gestation is not associated with an increased rate of GBS chorioamnionitis. There is no subgroup analysis for early gestations [86]. There is no equivalent evidence for women with known GBS carriage who have PPROM prior to 23^{+0} weeks of gestation.

Among women without GBS, the RCOG recommendation to delay birth until 37^{+0} weeks of gestation in the absence of an acute indication for birth (e.g., suspicion of chorioamnionitis, abruption, cord prolapse) is based on a Cochrane review that includes no women with PPROM prior to 28^{+0} weeks of gestation so the recommendation cannot be reliably extrapolated to this group [87]. There is no evidence on optimising timing of birth in women with PPROM prior to 24^{+0} weeks of gestation.

4.2 | Mode of Birth

4.2.1 | Prior to Viability

There is no evidence on safety of medical versus surgical TFMR in cases of PPROM. It should be noted that, while chorioamnionitis may complicate surgical termination, it does not contraindicate it and may be the safest way for some women to give birth [88]. Treatment dose antibiotics for chorioamnionitis should be considered for all women undergoing TFMR or having a second trimester pregnancy loss following PPROM given the extremely high rate of postnatal diagnosis (94%) [89].

Among women who have had an intrauterine death prior to 24^{+0} weeks of gestation, there is some evidence that dilatation and evacuation (D&E) is a safe alternative to induction of labour: a retrospective analysis of 136 women undergoing induction of labour for second trimester fetal indication TFMR or following intrauterine death versus 263 women undergoing D&E demonstrated a lower rate of complication in the D&E group (aOR for complications in the induction group 8.5, 95% CI 3.7–19.8; need for dilatation and curettage, or manual removal of the placenta (MROP) accounting for 80% of complications in the induction arm) [90]. However, it should be noted that women with rupture of the membrane were excluded from this study. It should be noted that average gestation at inclusion was between 18^{+0} and 20^{+0} weeks and whether these findings remain true closer to 24^{+0} weeks of gestation is not clear. Most significantly, the impact of cervical dilation is not considered in this work. Women must be counselled on the association between this and subsequent spontaneous preterm birth as part of the discussion related to risk of both procedures [91].

4.2.2 | At Viability

There is currently limited evidence regarding optimal mode of birth or use of intrapartum fetal monitoring in women labouring at periviable gestations. However, routine caesarean section is not recommended for the indication of periviable birth alone as it has not been shown to decrease mortality or intraventricular haemorrhage [92]. Of note, no analysis was carried out considering the implications of PPROM on complexity of birth at caesarean section or vaginal birth of extremely preterm infants, which would be of interest given that the absence of the amniotic sac may increase both the risk of bony injury at attempts to deliver vaginally or by caesarean, and also laceration to the fetus at uterine entry during caesarean section.

Evidence concerning the management of preterm labour with breech presentation is lacking. A retrospective study of 86 women delivering between 26^{+0} and 29^{+6} weeks of gestation revealed that planned caesarean birth was associated with fewer 5 min Apgar scores of <7, but no difference in neonatal mortality or major morbidity [93]. The same study demonstrated no statistically significant difference in the rates of head entrapment by mode of birth (13% and 6% for vaginal and caesarean respectively). The rate of neonatal death in cases where births had been complicated by head entrapment trended towards significance (4.8% and 0 for vaginal and caesarean birth respectively) [93], perhaps reflective of the surgical difficulty of lateral cervical incisions versus inverted T incision. Similarly to the above study, no analysis was carried out taking the impact of PPROM into account. Current RCOG recommendations to avoid routine amniotomy to reduce the risk of head entrapment, and lateral cervical incisions to relieve it should be followed at all viable gestations [94]. No studies focus on management of foetuses in transverse lie, although women must be counselled that (unlike at higher gestation) this is not an absolute indication for caesarean birth at periviability, and vaginal birth is achievable.

Regarding longer-term maternal risk following periviability caesarean birth, there is an increased risk of uterine rupture regardless of direction of uterine incision [95], and case report evidence suggests that this risk may be increased further if the woman then has a transabdominal cerclage [96].

4.3 | Placental Histopathology

In line with national guidance, the placenta must be sent to histopathology in all cases where PPROM has occurred prior to 24^{+0} weeks of gestation and birth occurs before 32^{+0} weeks of gestation, and gross and macroscopic analysis should be undertaken [97]. The histopathological findings associated with chorioamnionitis are given in Table 3. A placental swab sent for microscopy, sensitivity and cultures may aid in decisions surrounding antibiotics, particularly where there is no response to broad spectrum antibiotics, but it should be noted that a positive swab does not confer a diagnosis of histological chorioamnionitis (with positive swabs being a more common finding) [98]. Diagnosis is clinically useful in maternal and neonatal sepsis, and can inform care in future pregnancies.

TABLE 3 | Histopathological findings indicative of chorioamnionitis as per the Amsterdam Criteria [103].

Maternal inflammatory response	
Stage 1: acute subchorionitis or chorionitis	Grade 1: not severe
Stage 2: acute chorioamnionitis—polymorphonuclear leukocytes extend into fibrous chorion and/or amnion	Grade 2: severe—confluent polymorphonuclear leukocytes or subchorionic microabscesses
Stage 3: necrotising chorioamnionitis—karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis, and/or amnion basement membrane hypereosinophilia	
Fetal inflammatory response	
Stage 1: chorionic vasculitis or umbilical phlebitis	Grade 1: not severe
Stage 2: involvement of the umbilical vein and one or more umbilical arteries	Grade 2: severe—near-confluent intramural polymorphonuclear leukocytes with attenuation of vascular smooth muscle
Stage 3: necrotising funisitis	

While rates of chorioamnionitis following PPROM at all gestations are thought to be in the region of 17–58% [99], this rises to 94% in pregnancies delivering between 21^{+0} and 24^{+0} weeks of gestation [88]. Vascular lesions, such as subchorionic haematomas, are also more common in PPROM, and are inversely related to the presence of funisitis, suggestive of an alternative aetiology in some women [100]. There is no research comparing management of future pregnancies depending on identified placental lesions specifically following PPROM. However, two studies of fetal deaths (one from the UK and another from the Netherlands) found that chorioamnionitis may recur in subsequent pregnancies [101, 102].

5 | Cost Implications

While separate data on birth following PPROM is not available, the financial cost of preterm birth is significant, both in terms of immediate neonatal care and lifelong support for resulting morbidities including learning support. UK figures, based on cost estimates from 2006, suggest an annual cost of £2.9bn related to preterm birth [104]. More recent data from Australia, suggests that the cost of schooling is around £40 000 and £3700 more per year for extreme and late preterm birth respectively, as compared to term births [105]. In any instance, increasingly sophisticated neonatal care is likely to result in increased short- and long-term costs associated with preterm birth. The financial cost to the health service and to families following baby loss has not been well quantified. Clinicians should be aware of the often limited financial support available for families after baby loss and consider this as part of holistic care.

6 | Opinion

- There is a lack of high-quality evidence regarding maternal and fetal outcomes following PPROM prior to 24^{+0} weeks of gestation; this results in poorer counselling of women which is highlighted by the variation in the advice and care that women describe was offered to them. However, multidisciplinary healthcare teams can reduce this heterogeneity by ensuring the most up-to-date evidence is given to women and families, and being cautious when using existing tools that do not include PPROM or chorioamnionitis in their modelling of counselling. Healthcare professionals must be honest with women and families in all areas, including where evidence is lacking. Regardless of available evidence, counselling must always be compassionate and have women and their families at its core. Nonetheless, prediction of both maternal and perinatal outcome warrants high-quality investigation if counselling is to improve.
- There is minimal data on longer-term neonatal outcomes, and no data on outcomes later in infancy and childhood. Prospective, longitudinal data collection should be undertaken.
- Appropriate timing of interventions routinely offered when PPROM occurs at a viable gestation and weight (e.g., ACS and prophylactic antibiotics) are unclear and require high-quality, adequately powered research.
- PPROM prior to 24^{+0} weeks of gestation does carry a maternal mortality risk, and women who choose expectant management must be adequately counselled on symptoms of sepsis, the need for early presentation and the likely clinical plan if there were concerns about maternal sepsis. Women should be given a plan regarding where to attend if they are unwell or concerned, and this should only be somewhere that sees pregnant women regularly and is available 24/7.
- Regardless of outcome, PPROM carries a risk of poorer maternal mental health outcomes. The timing and type of intervention that best mitigates this must be studied, and be prioritised for translation into clinical practice once results are available. While this research is ongoing there should be integrated emotional support as part of the multidisciplinary team caring for women with PPROM prior to 24^{+0} weeks of gestation.
- An eventual aim of all this research must be co-ordinated care, nationally and internationally, based on national guidance developed with relevant stakeholders and improved by high-quality training of relevant healthcare professionals.

Conflicts of Interest

Full disclosure of interests are available at request.

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This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Dr. M Hall MRCOG, London; Dr. A Care MRCOG, Liverpool; Dr. L Goodfellow MRCOG, Liverpool; Dr. A Milan, London; C Curran, Little Heartbeats, Stockport; Dr. N Simpson MRCOG, Leeds; Prof A Heazell MRCOG, Manchester; Prof S Quenby MRCOG, Warwick; Prof AL David MRCOG, London; Prof A Shennan FRCOG, London; Dr. L Story MRCOG, London**.

The following organisations and individuals submitted comments at peer review:

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