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Care of Women with Preterm Prelabour Rupture of the Membranes Prior to 24 Weeks' Gestation

1. Scientific Impact Paper

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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 weeks of pregnancy (preterm), but the woman does not labour within 24 hours: this is preterm prelabour rupture of the membranes (PPROM). These women often give birth preterm. This paper looks at PPROM before 24 weeks of pregnancy. This happens in a much smaller number of women.

PPROM prior to 24 weeks is particularly concerning because of the chance of the baby being born extremely preterm. Babies born before 22 weeks cannot survive. Babies born between 22 and 26 weeks are at risk of severe and sometimes life-long problems. They also have a higher risk of dying than babies born later. Women sometimes develop an infection after PPROM, which can be extremely dangerous. If this happens, doctors will suggest ending the pregnancy even if the baby would not 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 and people who are pregnant. It is made more so 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 results 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 what problems individual women and babies might have. Finally, we look at evidence on the ways in which we can care for women and their babies up to delivery.

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.

1. Introduction

Preterm prelabour rupture of the membranes (PPROM) occurs when the fetal membranes rupture prior to 37 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 weeks' gestation, which has resulted in recent comprehensive clinical guidance,[1, 2] there is a paucity of evidence and guidance regarding optimal management of PPROM prior to this. PPROM at less than 24 weeks 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] In addition to the complexities surrounding management of pregnancies at risk of imminent delivery at the extremes of gestational age and birthweight,[4] PPROM at this gestation may be a clinical indication for termination of pregnancy for medical indication (TFMR).[2] Uncertainty surrounding clinical outcomes as well as complex management decisions also leaves women at high risk of psychological morbidity.[5, 6] There is no national guidance on this condition, and women who have experienced it describe significant variations in counselling and practice. Regarding language used in this guideline, previable delivery has a variable definition internationally based, but is taken to mean delivery prior to 22 completed gestational weeks. The evidence in this SIP 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 <24 weeks' gestation, and its implications for practice and future research. This is achieved via review of published literature and international guidance, and with collaboration from relevant patient groups.

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2. Outcomes of pregnancies following PPROM <24 weeks' 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 at the extremes of viability with the associated risks of neonatal death or long-term neurodisability, renders counselling complex - particularly concerning decisions for termination of pregnancy versus expectant management.

Of note, all research on PPROM is limited by diagnostic techniques utilised. 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 weeks. It has become clinical practice to use any of a number of commercially available bedside immunochromatographic tests where the diagnosis is equivocal.[7] However, evidence for these tests is lacking, with initial investigation often undertaken against now discredited tests, such as fern ing 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).[8] 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).[9] Ultrasound is not recommended 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 forwards 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 weeks' gestation prospectively collected data nationally from women with pregnancies complicated by PPROM prior to 23 weeks' gestation between 1st September 2019 and 28th February 2021 (a subgroup analysis was undertaken to consider the impact of the Covid-19 pandemic and no 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% (~55/10,000 women, both secondary to sepsis), although a 15-year analysis of the French Confidential Enquiries into Maternal Deaths gave a more conservative estimate

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with a previable PPROM attributable maternal mortality rate of 0.6/10,000, and a mortality rate among women with previable PPROM of 4.5/10,000 (95% CI 1.4-9.2) (previable defined as 14^{+0} to 24^{+6} gestational weeks).[10] 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. 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.[11]

A retrospective study from three institutions in the USA studied 208 women in three US institutions who experienced PPROM before 24 weeks' gestation between 2011-2018 and who either chose expectant management (51.9%) or TFMR (48.1%). Compared to women who chose TFMR, women who chose 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% delivered 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.[12] 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 weeks' gestation regardless of gestational age at delivery, 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,[4] thereby limiting its usefulness in this group. Latency to delivery is influenced by gestational age at PPROM (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 delivery 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 delivery rate in this group, including a 16% intrauterine death rate among cases delivered from 22^{+0} weeks' gestation onwards.

	Gestational weeks at preterm prelabour rupture of the membranes, n (%)			
Latency to delivery	16+0 – 17+6 n=43	18+0 – 19+6 n=70	20+0 – 21+6 n=80	22+0 – 22+6 n=30
<72 hours	16 (37)	18 (26)	20 (25)	6 (20)
72 hours 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 1: Latency to delivery 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).

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The UKOSS study findings highlighted that 31% of women elected to terminate (with the highest rate of termination seen in women who had PPROM at under 18 weeks' gestation) and 69% elected 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 termination were included within the analysis are a livebirth rate of 30-62% and a child survival to discharge without severe morbidity of 12-48%. Of note, there was no significant difference between morbidity outcomes of survivors of 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 weeks' gestation. Longer term outcomes are not available.

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	Gestational weeks at preterm prelabour rupture of the membranes, n(%)				
Outcome	16+0 – 17+6 n=84	18+0 – 19+6 n=102	20+0 – 21+6 n=107	22+0 – 22+6 n=37	p
Livebirth	14 (33)	27 (39)	37 (46)	20 (67)	0.023
Survival to discharge	17 (8)	16 (24)	21 (28)	10 (38)	0.265
Discharge without severe morbidity	5 (13)	11 (16)	13 (59)	9 (35)	0.127
Termination for medical reasons	39 (46)	32 (31)	25 (23)	7 (19)	0.004

Table 2: Neonatal outcome following preterm prelabour rupture of the membranes. (data from the UKOSS study).

Severe morbidity is defined as: grade 3-4 intraventricular haemorrhage or supplemental oxygen requirement at or beyond 36 weeks' postmenstrual age.

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An older retrospective single-centre study from The Republic of Ireland identified 42 women with PPROM before 24 weeks of gestation between 2007 and 2012 (when termination was not possible until the woman's life was in danger) indicated a livebirth rate of 24% but with only 5% of infants surviving to discharge.[3] Of note, mean gestation at membrane rupture was 18 weeks and delivery 20+5 weeks' gestation, as compared to 19+3 and 22+4 weeks' gestation (for women not having termination) 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 22-25 weeks' gestation and demonstrated a 10.5% and 36.0% survival to 2 years without cerebral palsy in babies where PPROM had occurred at 22 and 23 weeks' gestation respectively.[13] Another retrospective study (that excluded women undergoing termination of pregnancy) gives a 49% survival rate to discharge among neonates following PPROM at 20-24 weeks' gestation, with 47% of survivors experiencing severe neonatal morbidity; the mortality rate after discharge from neonatal care was not recorded.[14] One study compared outcomes of early (<25 weeks) and later (25-31 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.[15] 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 9,633 neonates born prior to 34 weeks' gestation with chorioamnionitis as compared to those without.[16]

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.[17] Given that formal diagnosis requires post-mortem assessment, postnatal identification is also challenging and largely based on secondary complications such as pulmonary hypertension or high oxygen requirements.[18] One systematic review of outcomes following PPROM prior to 24 weeks' 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 delivery 20-43 days). Although they note that this figure may under-represent true mortality as babies who died in the first 24 hours of life were less likely to have a clinical diagnosis prior to death.[19]

Amniotic fluid assessment has been investigated to determine risk of pulmonary hypoplasia. A prospective study of 580 women with PPROM between 20 and 28+0 weeks' gestation has demonstrated that a single deepest vertical pool (SDVP) of <2cm at presentation is associated with worse respiratory outcomes.[20] A smaller study of 31 women has suggested reduced neonatal survival where the SDVP is <1cm.[21] Both studies suggest that a higher SDVP increases latency to delivery, which could explain the improvement of respiratory and survival outcomes independent of the SDVP.

Two-dimensional ultrasound measures, such as the thoracic circumference, lung:head ratio[22] and quantitative lung index (= lung area/(head circumference/10)^2) have been evaluated as prognostic markers for pulmonary hypoplasia and poor outcome in fetuses with congenital diaphragmatic hernia.[23, 24] 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.[25] 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 post-mortem 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.[26] 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 and 27 weeks' gestation.[27] 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 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 weeks' gestation owing to reduced potential for fetal movements.[28] The prevalence of arthrogryposis associated with PPROM is not well documented: the UKOSS study reports two cases of 54 survivors with one or two limbs affected; a retrospective study of 130 neonates born following PPROM prior to 24 weeks' gestation describes a 29% rate of limb contractures;[14] larger studies of the aetiology of arthrogryposis demonstrates 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.[29]

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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).[30] 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,[29] whereas syndromic causes are more commonly associated with a need for surgeries.[31]

2.3.3 Prediction of maternal and fetal infection

While expedition of delivery 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 38^0C, it is non-specific in the absence of other symptoms, most of which are relatively insensitive (for example, maternal tachycardia 50-70% sensitive; foul smelling discharge 5-22% sensitive).[32] 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-minute gallium in glass test, which was most reliable overall.[33] 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;[32, 34-36] 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, 7]

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.[32] 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.[37] 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,[38] 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.[39]

Multiple studies have examined the intraamniotic environment via either amniocentesis or transvaginal collection of amniotic fluid following PPROM. Studies including women with PPROM prior to 24 weeks' gestation have suggested diagnostic utility of multiple markers including, but not limited to, interluekin-8,[40] matrix metalloproteinase-8,[41] monocyte chemoattractant protein-1 [42] and tumour necrosis factor-α.[43] In particular, interleukin-6 has been investigated, including on bedside immunochromatography, but not prior to 24 weeks' gestation.[43-46] 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.[47] 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 to 34 weeks' gestation compared those with and without a 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).[48] To our knowledge, no work undertaken at earlier gestational ages is available.

A meta-analysis of 12 studies of 1,744 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 weeks' gestation.[49] 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.[47] Studies are ongoing looking at the utility of MRI given promising differences in predicting delivery in women at high risk of delivery prior to 32 weeks' gestation.[50-52]

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.[53-56] 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.[57] 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' 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 weeks' gestation were found to have a significantly increased risk of complications (fetal or neonatal death, placental abruption, umbilical cord prolapse or delivery outside of a maternity unit) if managed as an outpatient (odds ratio [OR] 6.2, 95% confidence interval [CI] 1.6 - 23.8).[58] 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 delivery, women should be cared for 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 weeks' gestation is from a Cochrane review that demonstrates increased latency to delivery and reduction in short-term neonatal complications, without impact on maternal or neonatal mortality, or long-term infant outcomes when

antibiotics are given.[59] However, this study is all gestations, and there are no subgroup analyses by gestational age at PPROM; the numbers of women with PPROM prior to 24 weeks' gestation who are included is unclear.

The largest study to date of oral antibiotic use in PPROM recruited 4,826 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 latency to delivery of 48 hours, as well as a reduction in composite neonatal morbidity.[60, 61]

3.3 Antenatal corticosteroid and magnesium sulphate use

Evidence for the use of antenatal corticosteroids (ACS) prior to 24 weeks' gestation is lacking. One observational study carried out over 15 years demonstrated a reduction in death or neurodevelopmental delay in babies born at 23 weeks' gestation or later (68.4% versus 90.5%); the same was not true of babies born at 22 weeks' gestation.[62] There is no higher quality evidence than this. BAPM does not support universal use prior to 24 weeks' gestation.[4]

There is increasing evidence that administration of antenatal steroids close to time of delivery confers greatest risk reduction; therefore, ACS should ideally not be given more than seven days prior to delivery, 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 weeks' gestation, incorrect timing of steroids is likely to have a particularly detrimental effect. 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),[63] this has not been replicated in the most recent Cochrane review, which included 1 5 RCTs, including the ACT trial (OR 0.86, 95% CI 0.69-1.08).[64]

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

3.4 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 weeks' gestation demonstrated no maternal or neonatal benefit.[65] 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 deliveries, and 0.8 per 1000 deliveries respectively) without any obstetric benefit.[66] 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).[67] Nonetheless, current guidance would not insist upon LMWH[68] 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.

3.5 Management of pregnancies with cerclage in situ

Absolute indications for the removal of a cervical cerclage are no different in women prior to 24 weeks' gestation and include: confirmed labour, ongoing antepartum haemorrhage, maternal sepsis, fetal demise, and decision for imminent vaginal delivery.[69]

The best course of action for management of cerclage in women with PPROM prior to 24 weeks' 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 withing 48 hours in the retention group (OR 0.15, 95% CI 0.07-0.31), but decreased rates of chorioamnionitis and one minute 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).[70] Another review of multiple studies proposed that cerclage retention is associated with increased rates of maternal pyrexia and chorioamnionitis without improved latency.[71] 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).[72] 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 weeks' gestation.[73] No group has demonstrated neonatal benefit following cerclage retention or removal at time of PPROM.

3.6 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.[74] 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 hours would receive intrapartum antibiotics regardless of GBS status on swab..[7] 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. While this would be prudent at all gestations, investigation at early gestation may yield valuable information on balancing the risks of GBS sepsis and serious prematurity-associated morbidity.

3.7 Termination of pregnancy

The most recent UK data demonstrates that 31% of women with PPROM prior to 23 weeks' gestation will elect to undergo termination, with the decision being more common when PPROM occurs at earlier gestations. 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' gestation). Where feticide is not being performed, women should be advised of the risk of signs of life following delivery based on their gestation.[75]

3.8 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.[76] The AMNIPROM pilot study demonstrated feasibility of amnioinfusion studies, but highlighted longer term neonatal outcomes as necessary endpoints.[77] Trials are currently underway in Germany for the management of 2nd trimester PPROM with amnioinfusion.[78]

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.[79] In any circumstance, neither procedure should be offered outside of a clinical trial.

3.9 Emotional support

Women with PPROM are at higher risk of antenatal anxiety, postnatal depression and posttraumatic stress disorder.[5, 6, 80] Best therapies and management of this 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.

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3.10 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 DCDA twins and 10 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 delivery or intrauterine demise prior to 22^{+0}, highlighting the complexity in management of these cases. There is no evidence on relative outcomes when there is single twin PPROM with preserved amniotic fluid in the second twin.

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4. Intrapartum management

4.1 Optimum timing of delivery

There is histopathological evidence from a single-centre that delaying delivery until 34 weeks' gestation in women with known genital tract GBS colonisation who have PPROM from 23 weeks' gestation is not associated with an increased rate of GBS chorioamnionitis. There is no subgroup analysis for early gestations.[81] There is no equivalent evidence for women with known GBS carriage who have PPROM prior to 23 weeks' gestation.

Among women without GBS, the RCOG recommendation to delay delivery of women until 37 weeks' in the absence of an acute indication for delivery (e.g., suspicion of chorioamnionitis, abruption, cord prolapse) gestation is based on a Cochrane review that includes no women with PPROM prior to 28 weeks' gestation so the recommendation cannot be reliably extrapolated to this group.[82] There is no evidence on optimising timing of delivery in women with PPROM prior to 24 weeks' gestation.

4.2 Mode of delivery

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 to deliver for some women.[83] All women and people who are pregnant undergoing TFMR or having a second trimester pregnancy loss following PPROM should be offered treatment dose antibiotics for chorioamnionitis given the extremely high rate of postnatal diagnosis (94%).[84]

4.2.2 At viability

There is currently limited evidence regarding optimal mode of delivery or use of intrapartum fetal monitoring in women labouring at periviable gestations. However, routine Caesarean section is not

recommended for the indication of periviable delivery alone as it has not been shown to decrease mortality or intraventricular haemorrhage.[85] Of note, no analysis was carried out considering the implications of PPROM on complexity of delivery 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 at 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 and 29^{+6} days gestation revealed that planned Caesarean section was associated with fewer 5 minute Apgar scores of <7, but no difference in neonatal mortality or major morbidity.[86] The same study demonstrated no statistically significant difference in the rates of head entrapment by mode of delivery (13% and 6% for vaginal and Caesarean respectively). The rate of neonatal death in cases where deliveries had been complicated by head entrapment trended towards significance (4.8% and 0 for vaginal and Caesarean delivery respectively),[86] 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.[87] No studies focus on management of fetuses in transverse lie, although women must be counselled that (unlike at higher gestation) this is not an absolute indication for Caesarean section at periviability, and vaginal delivery is achievable.

Regarding longer term maternal risk following periviability Caesarean section there is an increased risk of uterine rupture regardless of direction of uterine incision,[88] and case series evidence suggests that this risk may be increased further if the woman then has a transabdominal cerclage. A summary of advice regarding neonatal care is given in Appendix 2 for information.

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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 weeks' gestation and delivery occurs before 32 weeks' gestation, and gross and macroscopic analysis should be undertaken.[89] 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).[90] Diagnosis is clinically useful in maternal and neonatal sepsis,and can inform care in future pregnancies. While rates of chorioamnionitis following PPROM at all gestations are thought to be in the region of 17-58%,[91] this rises to 94% in pregnancies delivering between 21 and 24 weeks.[84] 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.[92] 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.[93, 94]

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	

Table 3: Histopathological findings indicative of chorioamnionitis as per the Amsterdam Criteria.[95]

5. Cost implications

While separate data on delivery 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.[96] 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 deliveries [97] In any instance, increasingly sophisticated neonatal care is likely to result in increased short and long term costs associated with preterm birth.

5. Opinion

- There is a lack of high-quality evidence regarding maternal and fetal outcomes following PPROM prior to 24 weeks' gestation; this results in poorer counselling of women which is highlighted by the variation in advice and care that women describe was offered to them. However, healthcare professionals can reduce this heterogeneity by insuring most up-to-date evidence is given to patients, and being cautious when using existing tools that do not include PPROM or chorioamnionitis in their modelling of counselling. 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 outcome, 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 (for example, ACS and prophylactic antibiotics) are unclear and require high-quality, adequately powered research.
- PPROM prior to 24 weeks' 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.
- 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.
- 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.

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