

Premature Rupture of Membranes: Diagnosis and Management

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Rupture of the fetal membranes may happen at any time during pregnancy. It becomes a problem if the fetus is premature (preterm rupture of membranes) or, in the case of a mature fetus, if the period of time between rupture of membranes and the onset of labor is prolonged. Premature rupture of the fetal membranes (PROM) is one of the most common and controversial problems facing the obstetric clinician. The fetal membranes and the amniotic fluid that they encase have functions that are critical for normal fetal protection, growth, and development. The fluid environment allows full fetal movement, enhancing normal muscle development and growth. Besides encasing the amniotic fluid, the membranes also serve as an important barrier separating the sterile fetus and the amniotic fluid from a bacteria-laden vaginal canal and preventing prolapse of any intra-amniotic contents through the cervix, which often dilates somewhat prior to the onset of labor. Finally, the membranes also function as a repository for substrates for many critical biochemical processes, including storage of phosphoglycerolipids, which releases the precursors for prostaglandins. Thus, any disruption in the integrity of the amniotic cavity might potentially interrupt or interfere with any or all of these important functions.

The purpose of this document is to review the current understanding of premature rupture of membranes (PROM) and to provide management guidelines that have been validated by appropriately conducted outcome-based

research. There is some controversy over the optimal approaches to clinical assessment and treatment of women with term and preterm PROM. Management hinges on knowledge of gestational age and evaluation of the relative risks of preterm birth versus infection, abruptio placentae, and cord accident that could occur with expectant management. The risk factors, diagnosis, and management of PROM are discussed here. Additional guidelines on the basis of consensus and expert opinion also are included.

Definition and Incidence:

The definition of PROM is rupture of membranes before the onset of labor. Membranes rupture that occurs before 37 weeks of gestation is referred to as preterm PROM. Although term PROM results from the normal physiologic process of progressive membrane weakening, preterm PROM can result from a wide array of pathologic mechanisms acting individually or in concert (1). Preterm delivery occurs in approximately 12% of all births in the United States and is a major factor contributing to perinatal morbidity and mortality. Despite extensive research in this area, the rate of preterm birth has increased by 38% since 1981. Premature rupture of membranes (PROM) is a complication in approximately one third of preterm births. It typically is associated with brief latency between membrane rupture and delivery, increased potential for perinatal infection, and in utero umbilical cord compression. Because of this, both PROM at and before term can lead to significant perinatal morbidity and mortality (2). PROM occurs in 3% of pregnancies and is responsible for one-third of preterm births. The gestational age and fetal status at membrane rupture have significant implications in the etiology and consequences of PROM. An accurate assessment of gestational age and knowledge of maternal, fetal, and

neonatal risks are essential to appropriate evaluation, counseling, and care of patients with PROM.

Etiology and Risk factors:

Normal fetal membranes are extremely strong early in pregnancy, to the extent that they withstand rupture from early all acute non-penetrating forces. As term approaches, the fetal membranes are subjected to forces that cause them to become progressively weakened. The combination of stretching of the membranes with uterine growth and the frequent strain caused by normal uterine contractions and fetal movements may contribute to the weakening of the membrane. In addition, significant biochemical changes occur in the membranes near term, including a substantial decrease in the collagen content. Thus, at term PROM may be a physiologic variant rather than a pathologic event. The pathogenesis of PROM is not well understood. There are multiple etiologies, mechanical and physiological that probably share a final common pathway leading to membrane rupture.

Risk factors for PROM are similar to those for preterm labor. A history of PROM, genital tract infection, antepartum bleeding, and cigarette smoking have a particular strong association with PROM (3).

- Previous PROM - A history of previous PROM is a significant risk factor for recurrence. As an example, the Preterm Prediction Study, a large prospective study conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, observed that women with a history of PROM had a 13.5% rate of PROM in a subsequent pregnancy compared to 4.1% in women with no such history (4).
- Genital infection - It is the single most common identifiable

risk factor for PROM. Three lines of epidemiologic evidence strongly support this association: (a) women with PROM are significantly more likely than women with intact membranes to have pathogenic microorganisms in the amniotic fluid, (b) women with PROM have a significantly higher rate of histologic chorioamnionitis than those who deliver preterm without PROM, and (c) the frequency of PROM is significantly higher in women with certain lower genital tract infections (eg, bacterial vaginosis) than in uninfected women. Many of the microorganisms that colonize the lower genital tract have the capacity to produce phospholipases, which can stimulate the production of prostaglandins and thereby lead to the onset of uterine contractions. In addition, the host's immune response to bacterial invasion of the endocervix and/or fetal membranes leads to the production of multiple inflammatory mediators that can cause localized weakening of the fetal membranes and result in PROM. Genetic regulation of the host's immune and inflammatory response to infections associated with PROM. Antepartum bleeding - In more than one trimester increases the risk of PROM three to seven fold (5). PROM is also associated with increased risks of abruptio placentae and prolapse of the umbilical cord.

- Cigarette smoking - The risk of PROM among smokers is increased two to four-fold compared to non-smokers. The risk persists even after adjustment for other known risk factors for PROM, including infection.
- Other factors - Occasionally, other etiologies can be identified. Premature PROM is more commonly seen in the setting of polyhydramnios or incompetent cervix, or following such procedures as cervical cerclage or amniocentesis. Multiple gestation, abruptio placentae,

hydramnios, nutritional deficit, previous cervical operations or lacerations are usually shown to correlate with increased risk of PROM. No relationship has been shown between PROM and maternal age, parity, maternal weight or weight gain, trauma, or meconium.

Clinical Manifestations and Diagnosis:

The classic clinical presentation of PROM is a sudden "gush" of clear or pale yellow fluid from the vagina. However, many women describe intermittent or constant leaking of small amounts of fluid or just a sensation of wetness within the vagina or on the perineum. A clinical history suggestive of PROM should be confirmed by visual inspection or laboratory tests to exclude other causes of wetness, such as urinary incontinence, vaginal discharge, and perspiration. The best method of confirming the diagnosis of PROM is direct observation of amniotic fluid coming out of the cervical canal or pooling in the vaginal fornix. If amniotic fluid is not immediately visible, the woman can be asked to push on her fundus, Valsalva, or cough to provoke leakage of amniotic fluid from the cervical os. Digital examination should be avoided because it may decrease the latency period (ie, time from rupture of membranes to delivery) and increase the risk of intrauterine infection (6).

Nitrazine and Fern tests - if the diagnosis is not obvious after visual inspection, the diagnosis can be confirmed by testing of pH of the vaginal fluid, which is easily accomplished with nitrazine paper. Amniotic fluid has a pH range of 7.0 to 7.7 compared to the normally acidic vaginal pH of 3.8 to 4.2. False-negative and false-positive test results occur in up to 5% of cases. False negative tests results can occur when leaking is intermittent or the amniotic fluid is diluted by other

vaginal fluids. False positive results can be due to the presence of alkaline fluids in the vagina, such as blood, seminal fluid, soap, or some infections. A secondary confirmatory test is the presence of arborization (ferning). Fluid from the posterior vaginal fornix is swabbed onto a glass slide and allowed to dry for at least 10 minutes. Amniotic fluid produces a delicate ferning pattern, in contrast to the thick and wide arborization pattern of dried cervical mucus. Well-estrogenized cervical mucus or a fingerprint on the microscope slide may cause a false-positive fern test; false negatives can be due to inadequate amniotic fluid on the swab or heavy contamination with vaginal discharge or blood.

Ultrasonography - examination by ultrasound may be of value in the diagnosis of PROM. 50% to 70% of women with PROM have low amniotic fluid volume on initial ultrasonography (7). However, mild reduction of amniotic fluid volume is difficult to diagnose and has many etiologies. On the other hand, the finding of anhydroamnios or severe oligohydramnios combined with a characteristic history is highly suggestive of rupture of membranes, although renal agenesis, obstructive uropathy, or severe utero-placental insufficiency also can cause marked reductions in amniotic fluid volume.

Management:

The management of pregnancies complicated by PROM is based upon consideration of several factors, which are assessed upon presentation: gestational age; availability of neonatal intensive care; presence or absence of maternal/fetal infection; presence or absence of labor; fetal presentation; fetal heart rate (FHR) tracing pattern; likelihood of fetal lung maturity; cervical status (by visual, not digital, inspection unless induction is planned or the patient is in

labor).

Initial evaluation: Expedient delivery of women with PROM is indicated if intrauterine infection, abruptio placentae, repetitive fetal heart rate (FHR) decelerations, or a high risk of cord prolapse is present or suspected. In each of these conditions, fetal well-being can deteriorate with expectant management and there are no therapeutic interventions available other than delivery. In the absence of an indication for immediate delivery, swabs for diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* may be obtained from the cervix, if appropriate. The need for group B streptococci intrapartum prophylaxis should be determined if preterm PROM occurs. In patients with preterm PROM, electronic fetal heart rate monitoring and uterine activity monitoring offer the opportunity to identify occult umbilical cord compression and to evaluate for asymptomatic contractions. Biophysical profile test scores of 6 or less within 24 hours of delivery also have been demonstrated to correlate with positive amniotic fluid cultures and perinatal infection. It is important to remember that heart rate testing at less than 32 weeks of gestation may not yield a reactive result in an immature but otherwise healthy fetus. However, once a reactive result has been achieved, a subsequently non-reactive test should be considered suspicious.

Leakage of amniotic fluid after amniocentesis: When leakage of amniotic fluid occurs after amniocentesis, the outcome is better than after spontaneous preterm PROM. In studies involving women who had second-trimester amniocentesis for prenatal diagnosis of genetic disorders, the risk of PROM was 1-2%, and the attributable risk of pregnancy loss was 0.06%. In most patients, the membranes reseal with restoration of normal amniotic fluid volume.

Pre-viable premature rupture of membranes: The fetal

survival rate subsequent to PROM at 24-26 weeks of gestation has been reported to be approximately 57%. Significant maternal complications occurring after second trimester and pre-viable PROM have been to include intraamniotic infection, endometritis, abruptio placentae, retained placenta, and postpartum hemorrhage. Maternal sepsis is a rare but serious complication reported in approximately 1% of cases, and isolated maternal deaths due to infection have been reported in this setting. Outcomes of survivors of preterm PROM depend on the gestational age, presence of infection, length of latency, and other maternal and fetal complications. A variety of conditions associated with fetal lung compression or oligohydramnios or both can result in pulmonary hypoplasia. Reported risks of pulmonary hypoplasia after PROM at 16-26 weeks of gestation vary from less than 1% to 27%. Lethal pulmonary hypoplasia rarely occurs with membrane rupture subsequent to 24 weeks of gestation, presumably because alveolar growth adequate to support postnatal development already has occurred. Early second-trimester membrane rupture longer than 14 days are primary determinations of the risk of pulmonary hypoplasia. Prolonged oligohydramnios also is associated with in utero deformation, including abnormal facies (ie, low-set ears and epicanthal folds) and limb contractures and other positioning abnormalities (9).

Management of premature rupture of membranes chronologically (10):

Gestational Age

Management

Term (37 weeks or more)

Proceed to delivery, usually by induction of labor; Group B streptococcal prophylaxis recommended

Near term (34 weeks to 36 completed weeks)	Same as for term
Preterm (32 weeks to 33 completed weeks)	<p>Expectant management, unless fetal pulmonary maturity is documented;</p> <p>Group B streptococcus prophylaxis recommended;</p> <p>Corticosteroid – no consensus, but some experts recommend;</p> <p>Antibiotics recommended to prolong latency if there are no contraindications</p>
Preterm (24 weeks to 31 completed weeks)	<p>Expectant management;</p> <p>Group B streptococcal prophylaxis is recommended;</p> <p>Single-course corticosteroid use recommended;</p> <p>Tocolytics – no consensus;</p> <p>Antibiotics recommended to prolong latency if there are no contraindications</p>
Less than 24 weeks*	<p>Patient counseling;</p> <p>Expectant management or induction of labor;</p> <p>Group B streptococcal prophylaxis is not recommended;</p> <p>Corticosteroids are not recommended;</p> <p>Antibiotics, there are incomplete data on use in prolonging latency</p>

*The combination of birth-weight, gestational age and sex

provide the best estimate of chances of survival and should be considered in individual cases.

Role of tocolysis for the management of patients with preterm PROM:

Use of prophylactic tocolysis after preterm PROM has been shown to prolong latency in the short term, whereas the use of therapeutic tocolysis (ie, instituting tocolysis only after contractions have ensued) has not been shown to prolong latency. The use of tocolysis is controversial; there are inadequate data on which to make an evidence-based recommendation for or against their use. Tocolysis are unlikely to be effective in women with advanced labor. Many clinicians administer tocolytics for 48 hours to women at less than 32 weeks of gestation with contractions, but not in advanced labor, in an attempt to delay delivery to allow administration of antenatal glucocorticoids. Many centers use nifedipine (10 mg orally every 6 hours for 48 hours) for tocolysis. The effect of tocolysis to permit antibiotic and antenatal corticosteroid administration in the patient with preterm PROM who is having contractions has yet to be conclusively evaluated; therefore, specific recommendations for or against tocolysis administration cannot be made. A recent retrospective study compared the prolonged use of tocolysis for longer than 48 hours plus antibiotics and steroids with gestational age-matched infants not treated for PROM. The investigators concluded that chorioamnionitis and a latency of greater than 1 week achieved by prolonged use of tocolysis lessens the advantages of extended gestational age and decreased pre-discharge neonatal morbidity (11).

Antenatal corticosteroids administration to patients with preterm PROM:

The impact of antenatal corticosteroid administration after preterm PROM on neonatal outcomes has been evaluated in a number of clinical trials. The National Institutes of Health Consensus Development Panel has recommended a single course of antenatal corticosteroids for women with PROM before 32 weeks of gestation in the absence of intra-amniotic infection. Pregnancies treated with antenatal glucocorticoids have significant reductions in neonatal complications compared to untreated pregnancies: respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and there is a trend toward reduction in neonatal death. Treatment is not associated with an increase in maternal or neonatal infections. Glucocorticoids are given as late as 34 weeks of gestation to women with intact membranes at risk for preterm delivery (12). The use of glucocorticoids after 32 weeks in women with PROM is more controversial, as treatment at this gestational age has not consistently resulted in benefit. Most of the centers generally administer a course of antenatal glucocorticoids in such cases when there is documented fetal pulmonary immaturity and no evidence of chorioamnionitis. The risk of infection from corticosteroid use at 32-33 completed weeks of gestation is unclear, but based on available evidence; their use has been recommended by some experts, particularly if pulmonary immaturity is documented. Studies of the combined use of corticosteroids and prophylactic antibiotics after preterm PROM suggest significant reductions in respiratory distress syndrome (RDS), perinatal mortality, and other morbidities with no evident increase in perinatal infections after steroid administration.

Antibiotics administration to patients with preterm PROM:

The rationale for antibiotic prophylaxis is that infection

appears to be both a cause and consequence of PROM, and is related to preterm delivery. The goal of antibiotic therapy is to reduce the frequency of maternal and fetal infection and delay the onset of preterm labor (ie, prolong latency). The importance of reducing infection is understood by studies suggesting a relationship between chorioamnionitis, duration of membrane rupture, and development of cerebral palsy or neuro-developmental impairment. Based on available information, a 7-day course of parenteral and oral therapy with ampicillin or amoxicillin and erythromycin is recommended during expectant management of preterm PROM remote from term to prolong pregnancy and to reduce infectious and gestational age-dependent neonatal morbidity. Use of the combination of oral erythromycin and extended-spectrum ampicillin-clavulanic acid in women near term does not appear to be beneficial, may be harmful, and is not recommended. Antibiotic administration to prolong latency must be distinguished from well-established protocols directed at prevention of group B streptococcal infection in term and preterm patients (13). The prophylactic antibiotic regimen would appropriately treat group B streptococcal infections during expectant management of preterm PROM remote from term. However, women with PROM and a viable fetus, who are known carriers of group B streptococci and those who give birth before carrier status can be delineated, should receive intrapartum prophylaxis to prevent vertical transmission regardless of earlier treatments.

We administer a seven-day course of antibiotic prophylaxis to all women with PROM who are being managed expectantly. Our preference is to give ampicillin 2 g intravenously every six hours for 48 hours, followed by amoxicillin (500 mg orally three times daily or 875 mg orally twice daily) for an additional five days. In addition, we give a

single dose of azithromycin (one gram orally). This is given in lieu of a multiple day course of erythromycin, which has been recommended by others. The powder formulation of azithromycin is less expensive than the tablets, but may not be as well tolerated. Prophylactic antibiotics may exert selective pressures for emergence of drug-resistant microorganisms. In addition, there is theoretical concern that clinical infections may be more difficult to recognize or treat in patients who have received prophylactic antibiotics. These problems have not been observed in women with PROM receiving antibiotic prophylaxis. Women who develop overt infection require therapy with therapeutic, rather than prophylactic, antibiotics.

Patients with preterm PROM and a cervical cerclage:

There are no prospective studies available with which to guide the care of women with preterm PROM and a cervical cerclage in situ. Retrospective studies have found that removal of cerclage after PROM is associated with similar pregnancy outcomes to those with PROM but no cerclage. Cerclage retention after preterm PROM has been associated with trends toward increased maternal infectious morbidity, reaching statistical significance in one evaluation, and with only brief pregnancy prolongation. One study found increased infant mortality and sepsis-related death when the cerclage was left in place after PROM. One study found significant pregnancy prolongation with cerclage retention by comparing differing practices at two institutions; however, this could reflect population or practice differences at these institutions (14). Because the available studies are small and non-randomized, the optimal timing of cerclage removal is unclear. However, no controlled study has found cerclage retention after PROM to improve neonatal outcomes. The

risks and benefits of short-term cerclage retention pending completion of antenatal corticosteroid therapy to enhance fetal maturation have not been evaluated.

Method of delivery:

Cesarean delivery is performed for standard indications, otherwise labor is induced. If cervix is favorable, oxytocin is administered for induction according to standard protocols. Once cervical ripening has occurred, we prefer to use oxytocin over prostaglandins because oxytocin is more easily titrated. Misoprostol is also effective for inducing labor, and may be advantageous in women with unfavorable cervix.

Summary:

For women with PROM at term, labor should be induced at the time of presentation, generally with oxytocin infusion, to reduce the risk of chorioamnionitis. Patients with PROM before 32 weeks of gestation should be cared for expectantly until 33 completed weeks of gestation if no maternal or fetal contraindications exist. A 48-hour course of intravenous ampicillin and erythromycin followed by 5 days of amoxicillin and erythromycin is recommended during expectant management of preterm PROM remote from term to prolong pregnancy and to reduce infectious and gestational age-dependent neonatal morbidity. All women with PROM and a viable fetus, including those known to be carriers of group B streptococci and those who gave birth before carrier status can be delineated, should receive intrapartum chemoprophylaxis to prevent vertical transmission of group B streptococci regardless of earlier treatments. A single course of antenatal corticosteroids should be administered to women with PROM before 32 weeks of gestation to reduce the risks of RDS, perinatal mortality, and other morbidities.

Delivery is recommended when PROM occurs at or beyond 34 weeks of gestation. With PROM at 32-33 completed weeks of gestation, labor induction may be considered if fetal pulmonary maturity has been documented. Digital examinations should be avoided in patients with PROM unless they are in active labor or imminent delivery is anticipated. A specific recommendation for or against tocolysis administration cannot be made. The efficacy of corticosteroid use at 32-33 completed weeks is unclear based on available evidence, but treatment may be beneficial particularly if pulmonary immaturity is documented. For a woman with preterm PROM and a viable fetus, the safety of expectant management at home has not been established.

References:

1. Mercer BM. Preterm premature rupture of the membranes. *Obstet Gynecol* 2003;101:178-193. (Level III)
2. Martin JA, Hamilton BE, Sutton PD et al. Births: final data for 2004. *Natl Vital Stat Rep* 2006;5(1):1-101. (Level II-3).
3. Mathews TA, Mac Dorman MF. Infant mortality statistics from the 2003 period linked birth/infant death data set. *Natl Vital Stat Rep* 2006;5(1):1-101. (Level II-3)
4. Mercer BM, Goldberg RL, Moawad AH et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 2000;183:738-745. (Level II-2)
5. Moore RM, Mansour JM, Redline RW et al. The physiology of fetal membrane rupture: insight gained

- from the determination of physical properties. *Placenta* 2006;27:1037-1051. (Level II-3)
6. Alexander JM, Mercer BM, Miodovnik M et al. The impact of digital cervical examination on expectantly managed preterm rupture of membranes. *Am J Obstet Gynecol* 2001;183(4):1003-1007 (Level II-3)
 7. Mercer BM, Rabello YA, Thurnau GR et al. The NICHD-MFMU antibiotic treatment of preterm PROM study: impact of initial amniotic fluid volume on pregnancy outcome. NICHD-MFMU Network. *Am J Obstet Gynecol* 2006;194:438-445. (Level II-2)
 8. Lee SE, Park JS, Norwitz et al. Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes. *Obstet Gynecol* 2007;109:634-641
 9. Winn HN, Chen M, Amon E et al. Neonatal pulmonary hypoplasia and perinatal mortality in patients with midtrimester rupture of amniotic membranes - a critical analysis. *Am J Obstet Gynecol* 2000;182:1638-1644. (Level II-2)
 10. ACOG Practice Bulletin. Premature rupture of membranes. Number 80, April 2007
 11. Wolfensberger A, Zimmermann R, von Mandach U. Neonatal mortality and morbidity after aggressive long-term tocolysis for preterm premature rupture of membranes. *Fetal Diagn Ther* 2006;21:366-373. (Level II-2)
 12. Committee on, Obstetric Practice. ACOG committee opinion: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2002;99:871-873
 13. American College of Obstetricians and Gynecologists. Prevention of early-onset group B streptococci disease in newborns. ACOG Committee Opinion No. 289. *Obstet Gynecol* 2002;100:1405-1412. (Level III)

Jenkins TM, Berghella V, Shlossman PA et al. Timing of cerclage removal after preterm premature rupture of membranes: maternal and neonatal outcomes. *Am J Obstet Gynecol* 2000;183:847-852. (Level-II-3)