The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 217

(Replaces Practice Bulletin Number 188, January 2018)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Robert Ehsanipoor, MD and Christian M. Pettker, MD.

Prelabor Rupture of Membranes

Preterm birth occurs in approximately 10% of all births in the United States and is a major contributor to perinatal morbidity and mortality (1–3). Prelabor rupture of membranes (PROM) that occurs preterm complicates approximately 2–3% of all pregnancies in the United States, representing a significant proportion of preterm births, whereas term PROM occurs in approximately 8% of pregnancies (4–6). The optimal approach to assessment and treatment of women with term and preterm PROM remains challenging. Management decisions depend on gestational age and evaluation of the relative risks of delivery versus the risks (eg, infection, abruptio placentae, and umbilical cord accident) of expectant management when pregnancy is allowed to progress to a later gestational age. The purpose of this document is to review the current understanding of this condition and to provide management guidelines that have been validated by appropriately conducted outcome-based research when available. Additional guidelines on the basis of consensus and expert opinion also are presented. This Practice Bulletin is updated to include information about diagnosis of PROM, expectant management of PROM at term, and timing of delivery for patients with preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.

Background

The definition of *prelabor rupture of membranes* is rupture of membranes before the onset of labor. Membrane rupture before labor that occurs before 37 weeks of gestation is referred to as "preterm prelabor rupture of membranes." Management of preterm and term PROM is influenced by gestational age and the presence of complicating factors such as clinical infection, abruptio placentae, labor, or abnormal fetal testing. An accurate assessment of gestational age and knowledge of the maternal, fetal, and neonatal risks are essential to appropriate evaluation, counseling, and care of patients with PROM.

Etiology of Prelabor Rupture of Membranes

Membrane rupture may occur for a variety of reasons. Although membrane rupture at term can result from a normal physiologic weakening of the membranes combined with shearing forces created by uterine contractions, preterm PROM can result from a wide array of pathologic mechanisms that act individually or in concert (7, 8). Intraamniotic infection has been shown to be commonly associated with preterm PROM, especially at earlier gestational ages (9, 10).

A history of preterm PROM is a major risk factor for preterm PROM or preterm labor in a subsequent pregnancy (11–13). Additional risk factors associated with preterm PROM are similar to those associated with spontaneous preterm birth and include short cervical length, second-trimester and third-trimester bleeding, low body mass index, low socioeconomic status, cigarette smoking, and illicit drug use (14–17). Although each of these risk factors is associated with preterm PROM, the condition often occurs in the absence of recognized risk factors or an obvious cause.

Term Prelabor Rupture of Membranes

At term, PROM complicates approximately 8% of pregnancies and generally is followed by the prompt

onset of spontaneous labor and delivery (6). In a large randomized trial, one half of women with term PROM who were managed expectantly had an interval of membrane rupture to delivery of 33 hours, and 95% gave birth within 94–107 hours of membrane rupture with the use of oxytocin or prostaglandin when, during expectant management, induction was indicated or an endpoint of 4 days of expectant management was reached (18). The most significant maternal consequence of term PROM is intrauterine infection, the risk of which increases with the duration of membrane rupture.

Preterm Prelabor Rupture of Membranes

Regardless of obstetric management or clinical presentation, birth within 1 week of membrane rupture occurs in at least one half of patients with preterm PROM (8). Latency after membrane rupture is inversely correlated with the gestational age at membrane rupture (19). Cessation of amniotic fluid leakage with restoration of normal amniotic fluid volume may infrequently occur in the setting of spontaneous preterm PROM but can be associated with favorable outcomes (20–22).

Among women with preterm PROM, clinically evident intraamniotic infection occurs in 15–35% of cases and postpartum infection occurs in approximately 15–25% of cases. The incidence of infection is higher at earlier gestational ages (9, 23–25). Abruptio placentae complicates 2–5% of pregnancies with preterm PROM (26, 27).

The most significant risks to the fetus after preterm PROM are complications of prematurity. Respiratory distress has been reported to be the most common complication of preterm birth (28, 29). Sepsis, intraventricular hemorrhage, and necrotizing enterocolitis also are associated with prematurity but are less common near term. Preterm PROM has been associated with an increased risk of neurodevelopmental impairment (30–32), and early gestational age at membrane rupture also has been associated with an increased risk of neonatal white matter damage (33). However, there are no data that suggest that immediate delivery after presentation with PROM will avert these risks. A large cohort study suggests that prolonged latency duration, when adjusted for gestational age, does not worsen neonatal prognosis with respect to survival, survival without morbidity, and early-onset sepsis (34).

Periviable Prelabor Rupture of Membranes

Rupture of the membranes before viability occurs in less than 1% of pregnancies. The probability of neonatal death and morbidity associated with PROM decreases with longer latency and advancing gestational age (35, 36). In a review of periviable PROM occurring between 14 weeks of gestation and 24 weeks of gestation, perinatal deaths were more or less equally divided between stillbirths and neonatal deaths. Neonatal survival rates in patients expectantly managed for periviable PROM were much higher following membrane rupture after 22 weeks of gestation compared with membrane rupture before 22 weeks of gestation (57.7% versus 14.4%, respectively) (37). A second retrospective study of patients between 20 weeks of gestation and 24 weeks of gestation with periviable PROM who elected expectant management showed similar results, with neonatal survival of 22% of the newborns of patients with membrane rupture before 22 weeks of gestation and 58% for those with membrane rupture at 22 and 23 weeks of gestation (36). Most studies of second-trimester and periviable PROM are retrospective and include only expectantly managed cases. Thus, they likely overestimate survival rates because of selection bias. Survival data may vary by institution.

Significant maternal complications that occur after periviable PROM include intraamniotic infection, endometritis, abruptio placentae, and retained placenta (37). One center found that 14% of women with periviable PROM experienced significant maternal morbidity, including sepsis, transfusion, hemorrhage, infection, acute renal injury, and readmission (38). Although it occurs infrequently, life-threatening maternal infection may complicate expectant management of periviable PROM. Maternal sepsis is reported in approximately 1–5% of cases (36–38), and isolated maternal deaths due to infection have been reported in this setting.

Latency periods appear to be prolonged with second-trimester preterm PROM compared with PROM during later gestational ages. However, 40–50% of patients with periviable PROM will give birth within the first week and approximately 70–80% will give birth within 2–5 weeks after membrane rupture (36, 37, 39, 40).

The rate of pulmonary hypoplasia after preterm PROM before 24 weeks of gestation varies widely among reports and may be subject to variable reporting but is in the range of 2–20%. (35, 41–43). Pulmonary hypoplasia is associated with a high risk of mortality (37) but is rarely lethal when rupture of membranes occurs at or after 23–24 weeks of gestation (44), presumably because alveolar growth adequate to support postnatal development already has occurred. Early gestational age at membrane rupture and low residual amniotic fluid volume are the primary determinants of the incidence of pulmonary hypoplasia (46, 47). One retrospective cohort study demonstrated that persistent oligohydramnios in

cases of periviable PROM may correlate with lower survival rates and adverse neurodevelopmental outcomes (48). Prolonged oligohydramnios also can result in fetal deformations, including Potter-like facies (eg, low-set ears and epicanthal folds) and limb contractures or other positioning abnormalities. The reported frequency of skeletal deformations varies widely (1.5–38%) but many of these resolve with postnatal growth and physical therapy (37, 49).

Clinical Considerations and Recommendations

▶ *How is prelabor rupture of membranes diagnosed?*

Most cases of PROM can be diagnosed on the basis of the patient's history and physical examination. Examination should be performed in a manner that minimizes the risk of introducing infection. Because digital cervical examinations increase the risk of infection and add little information to results available with speculum examination, they generally should be avoided unless the patient appears to be in active labor or delivery seems imminent (50, 51). Sterile speculum examination provides an opportunity to inspect for cervicitis and prolapse of the umbilical cord or fetal parts, assess cervical dilatation and effacement, and obtain cultures as appropriate.

The diagnosis of membrane rupture typically is confirmed by conventional clinical assessment, which includes the visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a simple pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid, which is identified under microscopic evaluation. The normal pH of vaginal secretions is generally 3.8–4.5 whereas amniotic fluid usually has a pH of 7.1–7.3. False-positive test results may occur in the presence of blood or semen, alkaline antiseptics, certain lubricants, trichomonas, or bacterial vaginosis. Alternatively, false-negative test results may occur with prolonged membrane rupture and minimal residual fluid.

In equivocal cases, additional tests may aid in the diagnosis. Ultrasonographic examination of amniotic fluid volume may be a useful adjunct but is not diagnostic. Fetal fibronectin is a sensitive but nonspecific test for ruptured membranes; a negative test result suggests intact membranes, but a positive test result is not diagnostic of PROM (52). Several commercially available tests for amniotic proteins are currently on the market, with reported high sensitivity for PROM (53, 54). However, false-positive test result rates of 19–30% have been reported in patients with clinically intact membranes and symptoms of labor (55, 56). These tests are appealing in light of the requirements of regulatory bodies related to Clinical Laboratory Improvement Amendments of 1988 quality standards on the point-of-care methods of clinical assessment such as Nitrazine and fern testing. The studies evaluating these protein tests are problematic because most of them use conventional clinical assessment (pooling, ferning, pH) as controls or gold standards for the diagnosis of rupture of membranes, calling into question their utility in equivocal cases (53, 54, 57, 58). Additionally, the U.S. Food and Drug Administration released a letter to health care providers in response to adverse events related to their use, including 13 fetal deaths and multiple reports of health complications in pregnant women. The U.S. Food and Drug Administration letter reminded health care providers that these tests should not be used without other clinical assessments because of concerns about "misuse, overreliance, and inaccurate interpretation of lab test results from rupture of membranes tests used to detect rupture of membranes in pregnant women. These can lead to serious adverse events, including fetal death, infection, and other health complications in pregnant women." (59) At most these test kits should be considered selectively relative to standard methods of diagnosis.

If the diagnosis remains unclear after a full evaluation, and if the benefits of the procedure outweigh the risks, membrane rupture can be diagnosed with ultrasonographically guided transabdominal instillation of indigo carmine dye, followed by the passage of blue-dyed fluid into the vagina, which is documented by a stained tampon or pad that is removed 20–30 minutes later. It is important to note that maternal urine also will turn blue or blue-green and should not be confused with amniotic fluid. Recent shortages of indigo carmine dye have complicated the availability of this procedure, and alternatives, such as fluorescein, have been suggested (60).

▶ *What does initial management involve once prelabor rupture of membranes has been confirmed?*

In all patients with PROM, gestational age, fetal presentation, and fetal well-being (61) should be determined. The examination should evaluate for evidence of intrauterine infection and abruptio placentae. If results are not already available and if an indication for treatment is not already present, culture for group B streptococci (GBS) should be obtained when expectant management is being considered.

In patients with preterm PROM, an initial period of electronic fetal heart rate monitoring and uterine activity

monitoring offers the opportunity to identify abnormal fetal heart rate tracings and to evaluate for contractions (62). Management after confirmation of the diagnosis of PROM is dependent primarily on gestational age and is discussed in more detail in the following paragraphs. Abnormal fetal testing or evidence of intraamniotic infection are indications for delivery. Vaginal bleeding should raise concern for abruptio placentae, which should prompt consideration of delivery, with the decision based on fetal status, the amount of bleeding, and gestational age. In general, digital examination should be used sparingly and judiciously.

▶ *What is the optimal method of initial management for a patient with prelabor rupture of membranes at term?*

Gestational age and fetal position should be confirmed, and fetal heart rate monitoring should be used, to assess fetal status. Group B streptococcal prophylaxis should be given based on prior culture results or intrapartum risk factors if cultures have not been performed previously (63).

A meta-analysis of 23 randomized controlled trials (8,615 women) found that induction of labor reduced the time from rupture of membrane to birth and the rates of chorioamnionitis or endometritis, or both, and also reduced admission to the neonatal intensive care unit without increasing the rates of cesarean birth or operative vaginal delivery (6). The largest of these trials also found that women viewed induction of labor more positively than expectant management (18). Induction of labor with vaginal prostaglandins has been shown to be equally effective for labor induction compared with oxytocin but was associated with higher rates of chorioamnionitis (18). Infection also is a concern with mechanical methods of cervical ripening, such as the Foley catheter balloon, but there are insufficient data on which to base a firm recommendation for mechanical methods of cervical ripening in the setting of PROM. One trial comparing Foley catheter balloon with oxytocin to oxytocin alone in women with PROM demonstrated an increased risk with Foley balloon (8% compared with 0%, $P<.01$), though this was not seen in another similar trial (64, 65). A meta-analysis of four trials suggests that use of prophylactic antibiotics may reduce infection morbidity, but prompt induction of labor was not standard care in either study. Thus, there is insufficient evidence to justify the routine use of prophylactic antibiotics with PROM at term in the absence of an indication for GBS prophylaxis (66, 67).

Meta-analysis data indicate that patients with term PROM benefit from induction of labor compared with expectant management. Induction may help reduce infection in the woman and neonate without increasing the risk for cesarean birth (6). For women with PROM at 37 0/7 weeks of gestation or more, if spontaneous labor does not occur near the time of presentation in those who do not have contraindication to labor, labor induction should be recommended, although the choice of expectant management for a short period of time may be appropriately offered. In the cases in which expectant management is chosen, given that nearly 80% and 95% of patients start labor spontaneously within 12 hours and 24 hours respectively, a period of 12–24 hours of expectant management is reasonable as long as the clinical and fetal conditions are reassuring, and the patient is adequately counseled regarding the risks of prolonged PROM and the limitations of available data. For women who are GBS positive, administration of antibiotics for GBS prophylaxis should not be delayed while awaiting labor, and immediate induction rather than expectant management is recommended (63). During induction of labor with oxytocin, a sufficient period of adequate contractions (at least 12–18 hours) should be allowed for the latent phase of labor to progress before diagnosing failed induction and moving to cesarean birth (68–72).

▶ *When is delivery recommended for the preterm fetus in the presence of prelabor rupture of membranes?*

Abnormal results from fetal testing, clinical intraamniotic infection, and significant abruptio placentae are clear indications for delivery. Otherwise, gestational age is a primary factor when considering delivery versus expectant management (Box 1).

However, the optimal gestational age for delivery is unclear and controversial. A meta-analysis of 12 randomized controlled trials, including 3,617 women, concluded there was evidence to guide clinical practice toward expectant management regarding the risks and benefits of expectant management versus delivery in the setting of preterm PROM (73). Although there was no difference in neonatal sepsis between women who gave birth immediately compared with those managed expectantly, immediate birth had higher risks for neonatal respiratory distress, need for ventilation, neonatal mortality, neonatal intensive care unit admission, and likelihood of cesarean birth. In patients with no contraindications to continuing the pregnancy, such as abnormal results from fetal testing or intrauterine infection, expectant management likely provides benefit for the woman and newborn. Patients with preterm PROM before 34 0/7 weeks of gestation should be managed expectantly if no maternal or fetal contraindications exist (73, 74).

Box 1. Management of Prelabor Rupture of Membranes by Gestational Age Categories in Patients With Normal Antenatal Testing

Term (37 0/7 weeks of gestation or more)

- GBS prophylaxis as indicated
- Treat intraamniotic infection if present
- Proceed toward delivery (induction or cesarean as appropriate/indicated)

Late Preterm (34 0/7–36 6/7 weeks of gestation)

- Expectant management or proceed toward delivery (see text) (induction or cesarean as appropriate/indicated)
- Single-course of corticosteroids, if steroids not previously given, if proceeding with induction or delivery in no less than 24 hours and no more than 7 days, and no evidence of chorioamnionitis*
- GBS screening and prophylaxis as indicated
- Treat intraamniotic infection if present (and proceed toward delivery)

Preterm (24 0/7–33 6/7 weeks of gestation)

- Expectant management
- Antibiotics recommended to prolong latency if there are no contraindications
- Single-course of corticosteroids; insufficient evidence for or against rescue course
- Treat intraamniotic infection if present (and proceed to delivery)
- A vaginal–rectal swab for GBS culture should be obtained at the time of initial presentation and GBS prophylaxis administered as indicated.
- Magnesium sulfate for neuroprotection before anticipated delivery for pregnancies <32 0/7 weeks of gestation, if there are no contraindications†

Periviable (Less than 23–24 weeks of gestation)‡,§

- Patient counseling; consider neonatology and maternal–fetal medicine consultation
- Expectant management or induction of labor
- Antibiotics may be considered as early as 20 0/7 weeks of gestation
- GBS prophylaxis is not recommended before viability‖
- Corticosteroids are not recommended before viability‖
- Tocolysis is not recommended before viability‖
- Magnesium sulfate for neuroprotection is not recommended before viability†,‖

Abbreviation: GBS, group B streptococci.
*Do not delay delivery for steroids; steroids should not be administered for an imminent cesarean birth.
†Magnesium sulfate for neuroprotection in accordance with one of the larger studies.
‡The combination of birth weight, gestational age, and sex provide the best estimate of chances of survival and should be considered in individual cases.
§Periviable birth. Obstetric Care Consensus No. 6. American College of Obstetricians and Gynecologists. 2017;130:187–99.
‖May be considered for pregnant women as early as 23 0/7 weeks of gestation.

At 34 0/7 weeks of gestation and before 37 0/7 weeks of gestation, delivery has traditionally been recommended for all women with ruptured membranes. However, a recent large randomized trial of 1,839 women that evaluated immediate delivery (shortly after diagnosis and preferably within 24 hours) versus expectant management in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation suggests benefits to expectant management (75). Expectant management was according to local practice at participating centers, with 73% of patients managed in a hospital setting. There was no significant difference in the primary outcome—neonatal sepsis—or in the secondary outcome of composite neonatal morbidity. Infants in the immediate delivery group had higher rates of respiratory distress (relative risk [RR], 1.6; 95% CI, 1.1–2.3) and mechanical ventilation (RR, 1.4; 95% CI, 1.0–1.8) and spent more days in intensive care (4 days versus 2 days). However, maternal adverse outcomes, such as hemorrhage and infection, were approximately twofold higher with expectant management, although the rate of cesarean birth was lower (RR, 1.4; 95% CI, 1.2–1.7). According to the authors, the findings suggest that if expectant management is chosen, it should include careful monitoring of symptoms and signs of

maternal infection, chorioamnionitis, and antepartum hemorrhage. This monitoring may be done best in a hospital setting. An individual participant data meta-analysis of three trials showed similar results, with no difference in composite adverse neonatal outcome or neonatal sepsis when comparing expectant management with immediate delivery. In addition, immediate delivery resulted in higher rates of respiratory distress syndrome, intensive care admission, and cesarean birth (76). Either expectant management or immediate delivery in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation is a reasonable option, although the balance between benefit and risk, from both maternal and neonatal perspectives, should be carefully considered, and patients should be counseled clearly. Care should be individualized through shared decision making, and expectant management should not extend beyond 37 0/7 weeks of gestation. Latency antibiotics are not appropriate in this setting.

▶ *What general approaches are used in cases of preterm prelabor rupture of membranes managed expectantly?*

Expectant management of preterm PROM generally consists of hospital admission with periodic assessment for infection, abruptio placentae, umbilical cord compression, fetal well-being, and labor. There is no consensus on the optimal frequency of assessment, but an acceptable strategy would include periodic ultrasonographic monitoring of fetal growth and periodic fetal heart rate monitoring. A temperature elevation may indicate intrauterine infection. Prompt diagnosis of intraamniotic infection in preterm pregnancy requires a high index of suspicion because early signs and symptoms may be subtle. In the absence of fever, other clinical criteria, such as abdominal or fundal tenderness and maternal or fetal tachycardia, have variable sensitivity and specificity for diagnosing infection. Serial monitoring of leukocyte counts and other markers of inflammation have not been proved to be useful and are nonspecific when there is no clinical evidence of infection, especially if antenatal corticosteroids have been administered (77). Specific treatment considerations regarding tocolytics, corticosteroids, antibiotics, magnesium sulfate, and timing of delivery are discussed in detail below.

For cases of expectant management of periviable PROM, it is reasonable to evaluate and monitor such patients for a short period looking for signs of abnormalities as above. After a period of assessment in the hospital, outpatient management may be possible, as there is less concern for timely intervention for a periviable fetus. Expectant management of periviable PROM has significant maternal risks that are important to monitor carefully when choosing outpatient management. Such outpatient expectant management should involve frequent temperature evaluations, clear counseling on how to monitor for the signs and symptoms of abnormalities (eg, abdominal pain, vaginal bleeding, abnormal discharge), and frequent evaluations by a health care provider. Hospitalization often occurs around the time of viability when intervention for fetal indications is desired.

The use of 17-hydroxyprogesterone caproate to extend latency in cases of preterm PROM has been evaluated in two randomized trials. One trial involving 1,523 patients was stopped when a planned interim analysis suggested futility in continuing (78). There was no significant difference in interval to delivery or in composite adverse perinatal outcome, indicating that 17-hydroxyprogesterone caproate should not be used in patients with preterm PROM specifically for the purpose of extending latency. The second trial was stopped prematurely because of poor enrollment after 21 patients. This trial also did not find any benefit from 17-hydroxyprogesterone caproate (79). There are no data regarding the utility or safety of using vaginal progesterone in cases of preterm PROM. Given this lack of data and the theoretical risk of introducing infection with the administration of a daily vaginal drug in the presence of ruptured membranes, the use of vaginal progesterone is cases of preterm PROM is not recommended.

▶ *Should tocolytic agents be considered for patients with preterm prelabor rupture of membranes?*

The use of tocolytic agents in the setting of preterm PROM is controversial, and practice patterns among specialists vary widely (80). There are insufficient data to support or refute the use of tocolytic therapy in the setting of preterm PROM. A meta-analysis of eight trials evaluating the efficacy of tocolytic agents in preterm PROM is of limited use because women were only treated in two of the trials (81, 82) with latency antibiotics and corticosteroids, both of which have become part of standard management (83). The use of tocolytic therapy was associated with a longer latency period and a lower risk of delivery within 48 hours but also was associated with a higher risk of chorioamnionitis in pregnancies before 34 0/7 weeks of gestation. In summary, tocolytic agents may be associated with

a prolongation of pregnancy and an increased risk of chorioamnionitis without proven maternal or neonatal benefit, although their use has not been evaluated adequately with latency antibiotics and corticosteroids. In the setting of ruptured membranes with active labor, although tocolytic therapy has not been shown to prolong latency or improve neonatal outcomes, data are limited. Tocolytic agents can be considered in preterm PROM for steroid benefit to the neonate, especially at earlier gestational ages, or for maternal transport but should be used cautiously and avoided if there is evidence of infection or abruption. Tocolytic therapy is not recommended in the setting of preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.

▶ *Should antenatal corticosteroids be administered to patients with preterm prelabor rupture of membranes?*

The use of antenatal corticosteroids after preterm PROM has been evaluated in a number of clinical trials and has been shown to reduce neonatal mortality, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis (84–86). Current data suggest that antenatal corticosteroids are not associated with increased risks of maternal or neonatal infection regardless of gestational age. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks of gestation and 33 6/7 weeks of gestation and may be considered for pregnant women who are at risk of preterm birth within 7 days, including for those with ruptured membranes, as early as 23 0/7 weeks of gestation (87–89). A Cochrane meta-analysis reinforces the beneficial effect of this therapy regardless of membrane status and concludes that a single course of antenatal corticosteroids should be considered routine for all preterm deliveries (84).

Recent data indicate that administration of betamethasone in the late preterm period between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation reduces respiratory morbidity in newborns (90). Although a subgroup analysis was not done, approximately 22% of study patients had preterm PROM. A single course of corticosteroids is recommended for pregnant women between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation at risk of preterm birth within 7 days and who have not received a previous course of antenatal corticosteroids if proceeding with induction or delivery in no less than 24 hours and no more than 7 days (89). Late preterm administration of antenatal corticosteroids is not indicated in women diagnosed with clinical chorioamnionitis. Furthermore, delivery should not be delayed, and antenatal corticosteroids should not be used in the late preterm period (89).

There are no data that support the use of corticosteroids before viability, and administration of corticosteroids in this setting is not currently recommended. Weekly administration of corticosteroids has been associated with a reduction in birth weight and head circumference and is not recommended (91–93). Whether to administer a rescue course of corticosteroids with PROM at any gestational age is controversial, and there is insufficient evidence to make a recommendation for or against. A retrospective cohort study and a secondary analysis of a prospective cohort study suggest that corticosteroids do not increase the risk of chorioamnionitis (94, 95). If used as a rescue course, corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. A single repeat course of antenatal corticosteroids can be considered in women with preterm PROM who are less than 34 0/7 weeks of gestation, are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. However, delivery should not be delayed to achieve a rescue course.

▶ *Should magnesium sulfate for fetal neuroprotection be administered to patients with preterm prelabor rupture of membranes?*

Randomized controlled trials have demonstrated that maternal administration of magnesium sulfate used for fetal neuroprotection when birth is anticipated before 32 0/7 weeks of gestation reduces the risk of cerebral palsy in surviving infants (RR, 0.71; 95% CI, 0.55–0.91) (96). In the largest of these trials, 85% of the women enrolled had preterm PROM between 24 weeks of gestation and 32 weeks of gestation (97). Magnesium sulfate administration for this indication does not appear to affect latency interval (98). The optimal treatment regimen for fetal neuroprotection remains unclear, and different regimens were used in different trials. With respect to the use of magnesium sulfate for fetal neuroprotection, hospitals should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolytic therapy, and monitoring in accordance with one of the larger trials (97, 99, 100). Regardless of the treatment regimen used, women with preterm PROM before 32 0/7 weeks of gestation who are thought to be at risk of imminent delivery should be considered candidates for fetal neuroprotective treatment with magnesium sulfate (101).

▶ *Should antibiotics be administered to patients with preterm prelabor rupture of membranes?*

Administration of broad-spectrum antibiotics prolongs pregnancy, reduces maternal and neonatal infections, and reduces gestational age-dependent morbidity (23, 102, 103). The optimal antibiotic regimen is unclear because multiple regimens have demonstrated benefit. Based on available information, to reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation (23, 102). The regimen used in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial was intravenous ampicillin (2 g every 6 hours) and erythromycin (250 mg every 6 hours) for 48 hours followed by oral amoxicillin (250 mg every 8 hours) and erythromycin base (333 mg every 8 hours) (103). Some centers have replaced the use of erythromycin with azithromycin (such as a single oral dose of azithromycin 1 g) in situations in which erythromycin is not available or not tolerated, and this substitution is a suitable alternative (104, 105). One retrospective cohort study did not find a difference in latency or secondary outcomes such as neonatal survival, sepsis, or respiratory distress between the two medications (106). Another retrospective cohort study that also compared erythromycin and azithromycin likewise found no difference in latency (107). Further, there may be cost benefits to the use of azithromycin. (108) The use of amoxicillin–clavulanic acid has been associated with increased rates of necrotizing enterocolitis and it is not recommended (23, 102). Although there are no well-studied alternative regimens for women allergic to β-lactam antibiotics, it may be reasonable to consider another agent effective against GBS to replace the β-lactam agent. The choice of agent will be influenced by the severity of the reported allergic reaction and antibiotic susceptibility results of the GBS culture, if available (63). Patients with preterm PROM should be screened for GBS. Women with preterm PROM and a viable fetus who are candidates for intrapartum GBS prophylaxis should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier antibiotic treatments (63, 109). Approaches for GBS prophylaxis should emphasize appropriate principles of antibiotic stewardship.

▶ *Should preterm prelabor rupture of membranes be managed with home care?*

Two small randomized controlled trials that compared hospitalization to home care of women with preterm PROM had insufficient power to demonstrate a meaningful difference in outcome because only 11–18% of the women were eligible for antepartum home care (110, 111). Because latency is frequently brief, infection may present suddenly, and the fetus is at increased risk of umbilical cord compression, hospitalization with surveillance of the woman and her fetus is recommended once viability has been reached. The outpatient management of preterm PROM with a viable fetus has not been studied sufficiently to establish safety and, therefore, is not recommended. Periviable PROM may be considered for home care after a period of assessment in the hospital, as discussed previously.

▶ *How should a patient with preterm prelabor rupture of membranes and a cervical cerclage be treated?*

There are no complete prospective studies with which to guide the care of women with preterm PROM who have a cervical cerclage. One randomized trial that was terminated early because of concern regarding lack of power during the interim analysis failed to determine differences in outcomes between removal and retention of cervical cerclage in preterm PROM (112). Results from retrospective studies have not been consistent, but generally have found that cerclage retention for more than 24 hours after preterm PROM is associated with pregnancy prolongation (113). Because of the nonrandomized nature of the reports, it is unclear how factors, such as labor or infection, contributed to decisions for cerclage removal, which may have yielded biased results. In some, but not all studies, cerclage retention with preterm PROM has been associated with increased rates of neonatal mortality from sepsis, neonatal sepsis, respiratory distress syndrome, and maternal chorioamnionitis (113, 114). A firm recommendation regarding whether a cerclage should be removed after preterm PROM cannot be made, and either removal or retention is reasonable. Regardless, if a cerclage remains in place with preterm PROM, prolonged antibiotic prophylaxis beyond 7 days is not recommended.

▶ *What is the optimal management of a patient with preterm prelabor rupture of membranes and herpes simplex virus infection or human immunodeficiency virus?*

Neonatal herpes simplex virus (HSV) infection usually results from maternal–fetal transmission during delivery.

The risk of vertical transmission with delivery in patients with subclinical shedding at the time of labor as a result of having acquired genital HSV in the third trimester is reported to be between 30% and 50%, compared with only 3% in cases of maternal symptomatic reactivation of HSV at the time of labor (115). The literature regarding expectant management of preterm PROM with active maternal HSV infection is limited to small case series and case reports (116, 117). All patients were treated with acyclovir, and cesarean birth was performed if lesions were present at the time of delivery. No cases of vertical transmission were reported.

There is no consensus on the gestational age at which the risk of prematurity in women with preterm PROM outweighs the potential risk of neonatal HSV infection. In the setting of PROM with recurrent active infection, expectant management is recommended before 34 0/7 weeks of gestation. Antiviral therapy should be initiated when expectant management is elected, and corticosteroids, antibiotics, and magnesium sulfate for neuroprotection should be provided as clinically indicated. The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes. If active disease or prodromal symptoms are present at the onset of labor or when delivery is indicated, cesarean birth is recommended.

Optimal management of preterm PROM in the setting of primary HSV infection is less clear because of the increased risk of vertical transmission. Antiviral therapy is advocated, and if lesions are present at the time of delivery, cesarean birth is recommended. In general, cesarean birth is not recommended for women with a history of HSV infection but no active genital lesions or prodromal symptoms during labor (118). However, for women with a primary or nonprimary first-episode genital HSV infection during the third trimester of pregnancy, cesarean birth may be offered due to the possibility of prolonged viral shedding (119, 120).

The optimal management of the patient with human immunodeficiency virus (HIV) and preterm PROM also is uncertain because there are no adequate data from patients with prolonged rupture of membranes. Early observations showed that the duration of the interval between membrane rupture and labor correlated with risk of transmission to the newborn (121), but current data suggest that the duration the interval between membrane rupture and labor is not correlated with risk of vertical transmission in patients who receive highly active antiretroviral therapy, have a low viral load, and receive antepartum and intrapartum zidovudine (122, 123). Also, a series of 10 patients with preterm PROM who were managed expectantly while receiving antiretroviral therapy had no cases of HIV transmission to the newborn despite viral loads as high as 23,000 copies per mL. The latent periods ranged from 4 hours to 4 days in this series, and all had a cesarean birth (124).

The management of patients with HIV infection who have preterm PROM should be individualized with consideration of factors including gestational age, current antiretroviral regimen, and viral load. In cases involving a very early gestational age in which the patient is being treated with antiretroviral medications and the viral load is low, a period of expectant management is likely to be appropriate. In all cases, the patient should be managed in consultation with a physician with expertise in management of HIV in pregnancy. Furthermore, standard antepartum and intrapartum treatment guidelines should be followed, and management choices should be fully discussed with the patient (125).

▶ *How does care differ for patients with prelabor rupture of membranes that occurs before neonatal viability?*

Women presenting with PROM before neonatal viability should be counseled regarding the risks and benefits of expectant management versus immediate delivery. Counseling should include a realistic appraisal of neonatal outcomes (87). Immediate delivery (termination of pregnancy by induction of labor or dilation and evacuation) and expectant management should be offered. Physicians should provide patients with the most current and accurate information possible (87).

If the patient opts for expectant management and is clinically stable with no evidence of infection after evaluation, outpatient management and surveillance can be considered. Precautions should be reviewed with the patient, and the patient should come to the hospital if she develops symptoms of infection, labor, or abruptio placentae. Patients should monitor body temperatures. Typically, women with periviable PROM who have been cared for as outpatients are admitted to the hospital once the pregnancy has reached viability and the patient would accept interventions for delivery on behalf of the fetus.

Administration of antenatal corticosteroids and latency antibiotics for fetal maturation upon reaching viability is appropriate given that early delivery remains likely. Multiple ultrasonographic methods (such as thoracic measurements and ratios, flow velocities in pulmonary vessels, and three-dimensional estimations of lung volume) have been studied to evaluate pulmonary development in the antepartum period, but all are

of limited accuracy and cannot be considered sufficiently reliable for clinical management (47). Because most studies of antibiotic prophylaxis with preterm PROM enrolled patients only after 24 0/7 weeks of gestation, there are no adequate data to assess the risks and benefits of such treatment at earlier (periviable) gestational ages. However, it is reasonable to consider a course of broad-spectrum antibiotics for pregnancy prolongation in patients with periviable PROM who choose expectant management (87). There is no evidence to support the use of tocolytic agents in the setting of periviable PROM, and in this setting, it is not recommended.

▶ *What is the expected outcome of prelabor rupture of membranes after second-trimester amniocentesis?*

In studies of women undergoing second-trimester amniocentesis for prenatal diagnosis of genetic disorders, the risk of PROM is less than 1% (126–128). In contrast to patients with spontaneous PROM in the second trimester, reaccumulation of normal amniotic fluid volume and favorable outcomes are expected. In one series of 11 patients with periviable PROM after genetic amniocentesis, there was one periviable pregnancy loss, reaccumulation of normal amniotic fluid occurred within 1 month in 72% of patients, and the perinatal survival rate was 91% (126).

After appropriate counseling, patients with periviable PROM after genetic amniocentesis typically are managed expectantly as outpatients. Precautions regarding symptoms of chorioamnionitis and miscarriage should be given. Regular follow-up visits with ultrasonographic examinations to assess amniotic fluid volume are recommended.

▶ *How should a patient with a history of preterm prelabor of membranes be managed in future pregnancies?*

Patients with prior preterm PROM have an increased risk of recurrent PROM and preterm birth, and a detailed medical and obstetric history should be taken when patients have a history suggestive of these complications. However, there are few studies that examine interventions to prevent recurrent PROM. Women with prior preterm births should be counseled that short interpregnancy intervals, particularly those shorter than 6 months, may differentially and negatively affect subsequent pregnancy outcomes (129).

Patients with a history of preterm PROM were included in studies of progesterone supplementation for preterm birth recurrence reduction, but most studies did not report the specific proportion of women with PROM in the study group or separately analyze results in those patients (130, 131). However, given the potential benefit of progesterone therapy, women with a single gestation and a prior spontaneous preterm birth (due to either labor with intact membranes or preterm PROM) should be offered progesterone supplementation as clinically indicated to reduce the risk of recurrent spontaneous preterm birth.

Although vaginal ultrasonographic measurement of the cervix is a safe and reliable means of evaluating the risk of preterm birth related to cervical length, there have been no well-designed trials of cervical surveillance in women with a history of preterm PROM. Similar to the progesterone studies, trials that evaluated cervical assessment, vaginal progesterone, and cerclage included women with prior preterm PROM, but their specific data were not reported (132, 133). Thus, as with women with spontaneous preterm births, consideration can be given to transvaginal cervical length screening. Cerclage placement is associated with significant decreases in preterm birth outcomes, offers perinatal benefits, and may be considered in women with the following combination of history and ultrasonographic findings: a current singleton pregnancy, prior spontaneous preterm birth at less than 34 weeks of gestation, and short cervical length (less than 25 mm) before 24 weeks of gestation (134). There are no data on which to base a recommendation regarding the optimal gestational age for initiating surveillance or frequency of monitoring.

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- ▶ Patients with preterm PROM before 34 0/7 weeks of gestation should be managed expectantly if no maternal or fetal contraindications exist.
- ▶ A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks of gestation and 33 6/7 weeks of gestation and may be considered for pregnant women who are at risk of preterm birth within 7 days, including for those with ruptured membranes, as early as 23 0/7 weeks of gestation.
- ▶ A single course of corticosteroids is recommended for pregnant women between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation at risk of preterm birth within 7 days and who have not received a previous course of antenatal corticosteroids if proceeding with induction or delivery in no less than 24 hours and no more than 7 days.
- ▶ Women with preterm PROM before 32 0/7 weeks of gestation who are thought to be at risk of imminent

delivery should be considered candidates for fetal neuroprotective treatment with magnesium sulfate.

- To reduce maternal and neonatal infections and gestational-age-dependent morbidity, a 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin followed by oral amoxicillin and erythromycin is recommended during expectant management of women with preterm PROM who are at less than 34 0/7 weeks of gestation. Some centers have replaced the use of erythromycin with azithromycin in situations in which erythromycin is not available or not tolerated, and this substitution is a suitable alternative.
- Women with preterm PROM and a viable fetus who are candidates for intrapartum GBS prophylaxis should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier antibiotic treatments.

The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):

- For women with PROM at 37 0/7 weeks of gestation or more, if spontaneous labor does not occur near the time of presentation in those who do not have contraindication to labor, labor induction should be recommended, although the choice of expectant management for a short period of time may be appropriately offered.
- Either expectant management or immediate delivery in patients with PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation is a reasonable option, although the balance between benefit and risk, from both maternal and neonatal perspectives, should be carefully considered, and patients should be counseled clearly. Care should be individualized through shared decision making, and expectant management should not extend beyond 37 0/7 weeks of gestation. Latency antibiotics are not appropriate in this setting.
- In the setting of ruptured membranes with active labor, although tocolytic therapy has not been shown to prolong latency or improve neonatal outcomes, data are limited. Tocolytic agents can be considered in preterm PROM for steroid benefit to the neonate, especially at earlier gestational ages, or for maternal transport but should be used cautiously and avoided if there is evidence of infection or abruption. Tocolytic therapy is not recommended in the setting of preterm PROM between 34 0/7 weeks of gestation and 36 6/7 weeks of gestation.
- Given the potential benefit of progesterone therapy, women with a single gestation and a prior spontaneous preterm birth (due to either labor with intact membranes or preterm PROM) should be offered progesterone supplementation as clinically indicated to reduce the risk of recurrent spontaneous preterm birth.

The following conclusions are based primarily on consensus and expert opinion (Level C):

- The diagnosis of membrane rupture typically is confirmed by conventional clinical assessment, which includes the visualization of amniotic fluid passing from the cervical canal and pooling in the vagina, a simple pH test of vaginal fluid, or arborization (ferning) of dried vaginal fluid, which is identified under microscopic evaluation.
- The outpatient management of preterm PROM with a viable fetus has not been studied sufficiently to establish safety and, therefore, is not recommended. Periviable PROM may be considered for home care after a period of assessment in the hospital.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and March 2019. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

Published online on February 20, 2020.

American College of Obstetricians and Gynecologists
409 12th Street SW, Washington, DC 20024-2188

Prelabor rupture of membranes. ACOG Practice Bulletin No. 217. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;135:e80–97.

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