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Preterm Premature Rupture of the Membranes: Current Approaches to Evaluation and Management

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Preterm premature rupture of the membranes (PROM) complicates 3% of pregnancies and is responsible for approximately one third of all preterm births [1–4]. As a result, approximately 150,000 women suffer this pregnancy complication annually in the United States. Preterm PROM is associated with brief latency from membrane rupture to delivery. Particularly when PROM occurs remote from term, there are significant risks of infant morbidity and mortality after birth. Because of the association between PROM and intrauterine infection, oligohydramnios, and placental abruption, the fetus is also at risk before delivery, particularly if conservative management is attempted to prolong the pregnancy.

Because preterm PROM presents a clinical situation where early delivery is to be anticipated and prenatal and neonatal complications are common, the physician caring for women with this common obstetric disorder has an opportunity to intervene in a manner that can improve perinatal outcome. This article addresses clinically relevant questions regarding the evaluation and management of preterm PROM.

Why does preterm premature rupture of the membranes occur?

At term, membrane rupture is a normal part of parturition and can occur before or after the onset of contractions. This results from a combination of cellular apoptosis (programmed cell death), increased collagenase activity, and dissolution of the amniochorionic extracellular matrix, all of which can be exacerbated

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by contraction-induced shearing forces [5,6]. In many cases of preterm PROM, it is likely that the same physiologic processes are in place.

With decreasing gestational age of preterm PROM, however, it is more likely that membrane rupture is associated with an underlying pathologic process. Intrauterine infection, as demonstrated by positive amniotic fluid cultures and histologic chorioamnionitis, is common with preterm PROM, particularly with membrane PROM remote from term. It has been suggested that intrauterine infection results from ascending genital tract colonization, leading to increased cytokine activity that enhances membrane apoptosis, production of proteases, and dissolution of the membrane's extracellular matrix [7–9]. Mechanical stretch, as is seen with multiple gestations and polyhydramnios, may enhance local expression of cytokines to increase protease production and could also cause shearing strain on the membranes. Placental abruption could increase decidual-chorionic protease production and dissolution of the extracellular matrix through decidual thrombin expression. Clinical factors associated with PROM include low socioeconomic status and low maternal body mass index, prior preterm birth or preterm labor in the current pregnancy, maternal smoking, urinary tract and sexually transmitted infections, cervical conization or cerclage, and amniocentesis [1–10]. Ultimately, in many cases of preterm PROM, the actual cause of membrane weakening and rupture is not known. It is probable that a number of factors and a maternal genetic or physiologic predisposition act together to cause preterm PROM in many cases.

What is the typical clinical course after preterm premature rupture of the membranes?

Latency from membrane rupture to delivery is generally brief and is inversely proportional to gestational age at membrane rupture. Of all patients with ruptured membranes before 34 weeks of gestation, 93% deliver in less than 1 week [11]. Even with conservative management, at least one half of women deliver within a week of membrane rupture. When women with preterm PROM remote from term are given antibiotics during conservative management (see later), about one half of those remaining pregnant deliver in each subsequent week. Alternatively, a minority of women can benefit from extended latency with conservative management and a small proportion of women with membrane rupture can anticipate cessation of fluid leakage (2.6%–13%), particularly if PROM occurs as a complication of amniocentesis [12,13].

What are the maternal risks associated with preterm premature rupture of the membranes?

Women with preterm PROM and prolonged membrane rupture are at increased risk for chorioamnionitis, which may result from ascending bacterial

colonization before membrane rupture (causing PROM) or after membrane rupture (complicating PROM). The risk of infection increases with decreasing gestational age at membrane rupture [14,15], and with increasing duration of membrane rupture. In one study, 9% of women with PROM at term developed chorioamnionitis [16], and the risk increased to 24% with membrane rupture more than 24 hours. With PROM remote from term, chorioamnionitis is common (13%–60%), and postpartum endometritis complicates 2% to 13% of these pregnancies [17,18]. The incidence of placental abruption varies between studies (4%–12%) [19–21]. This is a significantly higher risk than the background population risk (approximately 1 in 200 pregnancies). Serious complications of PROM that have been reported with conservative management of PROM occurring early in pregnancy are retained placenta or postpartum hemorrhage necessitating dilation and curettage (12%); maternal sepsis (0.8%); and death (0.14%) [21].

What are the fetal and neonatal risks of preterm premature rupture of the membranes?

Fetal morbidity after preterm PROM results from maternal intrauterine infection, umbilical cord compression, placental abruption, and prolonged fetal compression caused by oligohydramnios. Each of these places the fetus at increased risk for fetal death (generally approximately 1% with conservative management after the limit of potential neonatal viability) and perinatal asphyxia. The pregnancy complicated by PROM before the limit of fetal viability (currently <23 weeks) is at increased risk for fetal demise (15%); however, a portion of this increase is attributable to nonintervention for fetal benefit when delivery occurs before there is any hope of postnatal survival. When membrane rupture occurs well before the limit of fetal viability (particularly when there is persistent oligohydramnios), there is a significant risk of lethal fetal pulmonary hypoplasia caused by arrested alveolar development. This becomes evident with failure of lung growth despite prolonged latency (see later). Prolonged compression can lead to fetal restriction deformities, similar to those seen in Potter's syndrome. There is accumulating evidence that in utero exposure to infection increases the risk of long-term neurologic sequelae [15], although there are not current data to demonstrate that delivery before the onset of clinical symptoms of infection prevents these adverse outcomes.

The primary determinant of infant morbidity and mortality is gestational age at delivery. In general, infant morbidity can be anticipated to be similar to that of other infants born at the same gestational age (absent pulmonary hypoplasia). Umbilical cord compression before and during labor and placental abruption, however, theoretically increase this risk of hypoxic insult. Additionally, the risk of neonatal infection is approximately twofold higher at any gestational age when delivery occurs after preterm PROM than for other causes. Group B streptococcus is a significant cause of early onset neonatal sepsis and is more likely to

occur in the setting of premature birth, prolonged membrane rupture, or amnionitis, each of which is seen commonly with preterm PROM. Lethal pulmonary hypoplasia is rare with PROM, occurring after 24 to 26 weeks' gestation, presumably because alveolar development by this time is adequate to support postnatal life. With PROM remote from term, however, there is the potential for nonlethal pulmonary hypoplasia, manifesting through postnatal pulmonary complications including pneumothorax, pneumomediastinum, and the need for high ventilatory pressures to compensate for poor pulmonary compliance.

In general survival is likely and long-term sequelae uncommon with delivery at or after 32 weeks' gestation (unless PROM occurs before 24–26 weeks' gestation). This is not a distinct cutoff, but rather a continuum with some infants doing well despite earlier delivery and a small number of infants having poor outcomes with delivery near term.

What are the most important determinants of management after preterm premature rupture of the membranes?

Under certain circumstances, delivery is indicated after preterm PROM, regardless of gestational age. Those with advanced labor, evident chorioamnionitis, nonreassuring fetal testing, overt fetal distress or demise, or significant bleeding from placental abruption require expeditious delivery, either vaginally or by cesarean section, as clinically appropriate. When there is significant cervical dilatation and fetal malpresentation, the risk of umbilical cord prolapse increases and may warrant delivery because of the increased risk of fetal loss despite early gestational age.

If the mother and fetus are clinically stable after initial assessment, gestational age is of primary importance in determining management. With preterm PROM, there is potential advantage to conservative management to prolong the latency from membrane rupture to delivery. The immature fetus can benefit if conservative measures prolong the pregnancy adequately to reduce gestational age–dependent morbidity. Alternatively, even brief pregnancy prolongation can benefit the immature fetus if active measures to enhance fetal maturation are undertaken (eg, maternal steroid administration). Once the fetus is mature, there is little to be gained from conservative management after membrane rupture.

What evaluations should be considered for women with preterm premature rupture of the membranes?

The first step in patient evaluation is confirmation of the diagnosis. In most cases, the diagnosis can be made based on history and physical examination. In the setting of a suspicious clinical history, the presence of Nitrazine-positive fluid ($pH > 6$) passing from the cervix is diagnostic. If the sterile speculum examination is equivocal, a specimen can be collected from the posterior fornix of the vagina

with a sterile swab. The swab is then applied to a microscope slide for visualization of ''arborized'' crystals under low-power microscopy after drying. False-positive results on Nitrazine testing can occur with blood or semen contamination, alkaline antiseptics, or bacterial vaginosis. The ferning test may be falsely positive if there is contamination with cervical mucous (generally nonbranching arborization). False-negative visual examination, ferning, or Nitrazine testing can occur with prolonged leakage with minimal residual fluid. If clinical suspicion remains after initial assessment, the patient can be retested after prolonged recumbency or alternate measures can be considered. A variety of ancillary techniques for confirmation of membrane rupture have been suggested (eg, cervicovaginal fetal fibronectin, human chorionic gonadotropin, maternal serum alpha fetoprotein, among others). These are nonspecific reflecting decidual disruption rather than membrane rupture. A negative test is likely reassuring, but a positive test does not confirm membrane rupture with certainty. Ultrasound evaluation should be performed if the diagnosis is suspected but cannot be confirmed clinically. Oligohydramnios without evident fetal urinary tract malformations or fetal growth restriction may be suggestive of membrane rupture, but is not diagnostic. The diagnosis can be made unequivocally with ultrasound-guided amnioinfusion of indigo carmine (1 mL in 9 mL of sterile normal saline). The passage of blue fluid per vagina onto a perineal pad is confirmatory.

Gestational age should be established based on clinical history and ultrasound. Ultrasound should estimate gestational age if no prior ultrasound has been performed. Even if prior ultrasound has been performed, ultrasound should be considered to assess fetal growth; position; residual amniotic fluid volume; and to identify gross fetal abnormalities, which may cause PROM by hydramnios. The patient should also be evaluated for evidence of advanced labor, chorioamnionitis, placental abruption, or fetal distress. Women with these complications require expeditious delivery.

At the time of initial speculum examination the cervix should be inspected visually for evident cervicitis or umbilical cord or fetal extremity prolapse. Cervical dilatation and effacement can be evaluated visually (correlation coefficient with digital examination, 0.74). To reduce the risk of infectious morbidity, digital examinations should be avoided unless delivery is expected [22]. Cervical cultures (eg, endocervical *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) are appropriate if not previously obtained. Anovaginal cultures for group B streptococcus (*Streptococcus agalactiae*) should be obtained if these have not been performed within the prior 6 weeks.

Where should conservative management be undertaken?

Unless delivery is immediately required, the patient with preterm PROM is best served by care in a facility capable of providing emergent delivery for maternal complications, such as placental abruption, fetal malpresentation in labor, or fetal distress caused by umbilical cord compression or in utero infection.

The facility should also be capable of providing emergent neonatal resuscitation and intensive care. If the initial facility lacks these capabilities, and delivery is not imminent, the patient should be transferred before additional complications occur.

How should the patient with preterm premature rupture of the membranes near term (32–36 weeks) be managed?

The potential for severe acute neonatal morbidity and mortality is low when delivery occurs at 34 to 36 weeks' gestation [23]. Corticosteroids are generally not given to accelerate fetal pulmonary maturity after 34 weeks. Conservative management of PROM at 34 to 36 weeks increases the risks of chorioamnionitis (16% versus 2%, $P = .001$) and lower umbilical cord blood pH (7.35 versus 7.25, $P = .009$), and increases maternal hospital stay (5.2 versus 2.6 days, $P = .006$). Such management has not been shown to significantly reduce neonatal morbidity [24]. Women with PROM at 34 to 36 weeks' gestation should be delivered expeditiously. It is appropriate to transfer these women, before delivery, to a facility capable of caring for an infant delivered at this gestation.

At 32 to 33 weeks' gestation, neonatal survival with immediate delivery is likely. There remains a risk, however, of respiratory distress syndrome (RDS) and other gestational age–dependent morbidities should fetal pulmonary maturity testing be immature. If fetal maturity testing is positive, however, the likelihood of pulmonary and other acute major morbidities is low. In a study of PROM at 32 to 36 weeks' gestation, Mercer et al [25] found no cases of RDS, intraventricular hemorrhage, or necrotizing enterocolitis occurred with documented fetal pulmonary maturity at 32 to 36 weeks' gestation. Alternatively, in that population conservative management prolonged pregnancy only briefly (36 versus 14 hours, $P < .001$); increased the risk of chorioamnionitis (27.7% versus 10.9%, $P = .06$); and increased the risk for occult cord compression, without reducing neonatal morbidity [25]. Similar patterns were seen for those with PROM at 32 to 33 weeks' gestation. In a similar study among a higher-risk population at 30 to 33 weeks' gestation, Cox et al [26] found conservative management prolonged latency only briefly (59% versus 100% delivered at 48 hours, $P < .001$), and increased the risk of chorioamnionitis sevenfold (15% versus 2%, $P = .009$) with no evident reduction in gestational age–dependent morbidity, when tocolysis, antibiotics, and antenatal corticosteroids were not given [26]. In addition, there was one stillbirth caused by suspected occult umbilical cord compression.

When PROM occurs at 32 to 33 weeks' gestation, fetal pulmonary maturity testing should be attempted, if feasible. This can be obtained from vaginal pool or amniocentesis specimens if residual fluid permits. Phosphatidyl glycerol, fetal lung maturity-testing, and lecithin-sphingomyelin ratios are appropriate in this setting. Blood and meconium may lead to falsely immature results, so a mature result is reassuring. Alternatively, if there is significant blood or meconium present, serious consideration should be given to delivery rather than conservative management. If fetal pulmonary maturity is documented, it is generally

best to proceed to delivery before infectious complications ensue. If fetal pulmonary immaturity is suspected at 32 to 33 weeks, or should fluid for testing be unavailable, conservative management with close fetal monitoring, adjunctive antibiotic therapy, and antenatal corticosteroid administration (see later) is appropriate. If there is no plan either to induce fetal maturation with corticosteroids or to prolong pregnancy and suppress infection with concurrent antibiotics, however, these patients may be better delivered expeditiously before additional complications occur because extended latency is not likely.

What should be done after corticosteroid benefit has been achieved with antenatal corticosteroids at 32 to 33 weeks gestation?

Once corticosteroid benefit has been achieved after 48 hours of conservative management (see later), the remaining potential for fetal-neonatal benefit is limited unless extended latency of 1 week or more is anticipated. Data regarding the optimal time to discontinue conservative management of PROM are limited. Many physicians proceed to delivery at 34 weeks' gestation. In this scenario, women achieving the benefit of antenatal corticosteroids greater than 33 weeks and 0 days do not accrue benefits of extended latency with delivery a few days later at 34 weeks' gestation, but do incur the risks of chorioamnionitis, umbilical cord compression, and placental abruption. These women are likely best served by delivery once corticosteroid benefit has been achieved. Alternatively, for women with PROM before 33 weeks, or who are cared for at an institution that attempts to prolong latency further than 34 weeks, ongoing conservative management may be appropriate. An alternative approach to management of the woman with PROM at 32 to 33 weeks' gestation is to deliver 24–48 hours after antenatal corticosteroid administration to maximize the benefits of corticosteroid administration and avert the risk of subsequent complications.

How should the patient with premature rupture of the membranes remote from term (before 32 weeks' gestation) be managed?

Delivery before 32 weeks' gestation is associated with a significant risk of severe neonatal morbidities and death. In the absence of indications for delivery, women with preterm PROM at 23 to 31 weeks should be managed conservatively to prolong pregnancy and reduce the risk of gestational age–dependent morbidity. Examples of exceptions to this approach are fetal malpresentation, such as transverse lie-back up with coexisting advanced cervical dilatation; maternal HIV; and primary maternal herpes simplex virus infections. These circumstances increase the risks of fetal death caused by cord prolapse and compression, and maternal-fetal transmission, respectively.

After initial assessment, a period of prolonged fetal heart rate and maternal contraction monitoring is recommended to identify umbilical cord compression

or nonplacental contractions. These patients should be admitted to a facility capable of providing emergent delivery for placental abruption, fetal malpresentation in labor, or fetal distress caused by umbilical cord compression or in utero infection. If testing is reassuring, and the patient does not require transfer to another facility, the patient can be monitored on an inpatient antepartum ward. Bed rest in pregnancy may increase the risk of deep venous thrombosis. Leg exercises, antiembolic stockings, or prophylactic doses of subcutaneous heparin may be helpful for those on prolonged bed rest [27]. Digital pelvic examinations increase the risk of amnionitis and decrease latency, and should be avoided unless progressive labor is demonstrated or delivery is indicated. Fetal heart rate and uterine contraction monitoring should be performed at least daily because of the risk of umbilical cord compression and fetal demise [28]. Biophysical profile testing may be confounded by oligohydramnios but can be helpful should the nonstress test be equivocal. If testing reveals intermittent mild umbilical cord compression but otherwise reassuring fetal testing, continuous fetal heart rate monitoring should be considered if the patient is not to be delivered. The clinical findings should be reassessed 24 to 48 hours after antenatal corticosteroid administration and delivery considered if intermittent cord compression persists or other nonreassuring findings are evident. Oligohydramnios (low initial amniotic fluid index or maximum vertical amniotic fluid pocket <2 cm) has been associated with brief latency and with increased risk of amnionitis. Amniotic fluid volume does not accurately predict pregnancy outcome, however, and should not be used in deciding whether to attempt conservative management.

Findings suggestive of intrauterine infection should lead to consideration of delivery. Typical findings include the combination of fever greater than or equal to 100.4°F, uterine tenderness, or maternal or fetal tachycardia in the absence of another source of infection. An elevated maternal white blood cell count is supportive of suspicious clinical findings, but may be artificially elevated by recent antenatal corticosteroid administration (within 5–7 days). In general, routine maternal white blood cell counting is not needed. After initial evaluation on admission, follow-up testing can be considered if clinical findings are suspicious but equivocal. Additional supportive information can be obtained through amniocentesis. Amniotic fluid glucose concentration below 16 to 20 mg/dL, a positive Gram stain, or a positive amniotic fluid culture is also suggestive of intra-amniotic infection [29–31].

Can the patient with preterm premature rupture of the membranes be managed as an outpatient?

Hospitalization is generally indicated during conservative management of preterm PROM. Hospitalization encourages bed rest and pelvic rest, and allows frequent evaluation of maternal and fetal condition. In most cases, latency is relatively brief. For those with prolonged latency, however, there remains an increased risk of umbilical cord compression, fetal demise, and intrauterine

infection. It has been suggested that health care costs could be reduced through discharge of the stable gravida [32]. The study was small, however, and lacked the power needed adequately to evaluate fetal, infant, and maternal morbidities. In the absence of data confirming a lack of risk with outpatient management after the limit of potential viability, this practice is discouraged. Further study regarding the risks and benefits of home care after preterm PROM is warranted.

When PROM occurs before the limit of potential viability, outpatient management may be appropriate provided the patient has access to hospital and is compliant to pelvic and modified bed rest. Initial inpatient observation may increase the opportunity for membrane resealing, and allows early identification of infection, fetal demise, or abruption. Generally, if discharged after initial observation, these patients are readmitted at the limit of viability for closer monitoring of maternal and fetal status.

How does pulmonary hypoplasia occur and how is it diagnosed?

PROM occurring before the limit of viability, particularly that occurring before 20 weeks' gestation, is associated with a significant risk of fetal pulmonary hypoplasia. A number of theories have been proposed regarding the mechanism of pulmonary hypoplasia. It is probable, however, that intrauterine pressure supports the tracheobronchial tree, and that either local pulmonary or amniotic fluid factors support alveolar development. Membrane rupture leads to pulmonary collapse with subsequent arrest in alveolar development. This model is supported by animal studies in which amniorrhexis resulted in fetal pulmonary hypoplasia, but amniorrhexis with concurrent tracheal clipping did not.

The process of pulmonary hypoplasia is one that takes time to become apparent subsequent to the initial insult. Over a period of weeks, the lungs fail to grow in pace with the remainder of the fetus. This is manifest on ultrasound as a lag in chest circumference, chest-abdomen ratio, or lung length, among other indirect parameters of pulmonary growth [15,33,34]. Because the lag in lung growth likely reflects the results of an earlier insult rather than an ongoing process, it is unlikely that earlier delivery enhances outcome once pulmonary hypoplasia is suspected.

A variety of treatments to seal the membrane leak (eg, amnioinfusion, and fibrin-platelet-cryoprecipitate or gel-foam sealing) after PROM before viability have been attempted [35–37]. The efficacy and risks of these approaches have not been adequately evaluated to suggest their incorporation into clinical practice.

What are the considerations regarding group B streptococcus prophylaxis after premature rupture of the membranes?

The benefits of intrapartum prophylaxis with intravenous penicillin to prevent maternal-fetal transmission of group B streptococcus (*S agalactiae*) have been

well demonstrated [38]. Preterm birth and prolonged membrane rupture are both risk factors for neonatal group B streptococcus sepsis. The patient with preterm PROM should receive intrapartum group B streptococcus prophylaxis unless there is an available recent negative anovaginal culture. Known group B streptococcus carriers should receive intrapartum group B streptococcus prophylaxis regardless of prior treatment. Treatment consists of intravenous penicillin as a 5 million unit initial bolus followed by 2.5 million units every 4 hours, or ampicillin, 2 g then 1 g every 4 hours. Women who are penicillin allergic should be treated with intravenous cefazolin (2 g then 1 g every 8 hours) unless the patient is at significant risk for anaphylaxis or complications should anaphylaxis occur. Under that circumstance, either 500 mg intravenous erythromycin every 6 hours or 900 mg intravenous clindamycin every 8 hours should be given if sensitivity has been demonstrated. In the presence of significant anaphylaxis risk with penicillin and evident resistance to erythromycin or clindamycin, 1 g vancomycin should be given intravenously every 12 hours. The patient who has had a negative anovaginal culture within 6 weeks does not require intrapartum antibiotics unless there is evidence of chorioamnionitis or another medical condition requiring treatment.

Should antibiotics be given to prolong pregnancy and reduce infant morbidity?

This is perhaps one of the best studied areas regarding the treatment of preterm PROM. Over two dozen studies have been published regarding this issue, and most of these have been prospective randomized trials. The goal of adjunctive antibiotic therapy during conservative management of preterm PROM remote from term is to treat or prevent ascending decidual infection to prolong pregnancy and prevent amnionitis and reduce the risk of neonatal sepsis. These studies have been reviewed in a number of meta-analyses and recent publications [12,39,40]. In summary, broad-spectrum antibiotic treatment of conservatively managed women with PROM remote from term prolongs pregnancy, reducing the risk of delivery at 1, 2, and 3 weeks by half. Further, such treatment has been shown to reduce maternal chorioamnionitis, neonatal sepsis, and intraventricular hemorrhage, in addition to reducing the need for neonatal oxygen and surfactant therapy [40].

What is the optimal antibiotic regimen during conservative management of premature rupture of the membranes remote from term?

A number of different antibiotic regimens have been considered in trials addressing this issue. Ultimately, the goal is to provide antibiotic coverage against a range of gram-positive and gram-negative organisms that have been

demonstrated in intra-amniotic infections after PROM [21]. At the same time, there is a desire to limit the duration of therapy in the belief that this reduces selection of resistant organisms. Two large multicenter trials highlight different approaches to this issue [41,42]. The National Institutes of Child Health and Human Development Maternal Fetal Medicine Research Units (NICHD-MFMU) Network study of PROM from 24 to 32 weeks' gestation used initial aggressive intravenous therapy (48 hours) with ampicillin (2 g intravenously every 6 hours) and erythromycin (250 mg intravenously every 6 hours), followed by limited duration oral therapy (5 days) with amoxicillin (250 mg orally every 8 hours) and enteric coated erythromycin-base (333 mg orally every 8 hours). These agents provide broad-spectrum antimicrobial coverage and have demonstrated safety when used in pregnancy. Group B streptococcus carriers were treated with ampicillin for 1 week and then again in labor [41,43]. Another multicenter study (The ORACLE trial) included four study arms assigned to oral erythromycin, amoxicillin-clavulanic acid, both, or placebo for up to 10 days after preterm PROM occurring before 37 weeks [42].

The NICHD-MFMU study of PROM from 24 to 32 weeks found that antibiotic treatment increased twofold the likelihood that women would remain undelivered after 7 days of treatment, and that this effect persisted for up to 3 weeks after discontinuation of antibiotics at day 7 [41,43]. These data confirm that antibiotics improved neonatal outcomes including reductions in composite morbidity (one or more of death, RDS, early sepsis, severe intraventricular hemorrhage, or severe necrotizing enterocolitis: 44% versus 53%, $P < .05$), and also individual morbidities, such as RDS (40.5% versus 48.7%), severe necrotizing enterocolitis (2.3% versus 5.8%), patent ductus arteriosus (11.7% versus 20.2%), and chronic lung disease (bronchopulmonary dysplasia: 13% versus 20.5%) ($P \leq .05$ for each). Antibiotic treatment also reduced the incidences of amnionitis (23% versus 32.5%, $P = .01$) and neonatal group B streptococcus sepsis (0% versus 1.5%, $P = .03$). Neonatal sepsis (8.4% versus 15.6%, $P = .009$) and pneumonia (2.9% versus 7%, $P = .04$) were reduced in those who were not group B streptococcus carriers (group B streptococcus carriers received ampicillin even if assigned to placebo).

The ORACLE trial revealed brief pregnancy prolongation (not significant at 7 days), and decreased need for supplemental oxygen (31.1% versus 35.6%, $P = .02$) and positive blood cultures (5.7% versus 8.2%, $P = .02$), but no significant reduction in the primary outcome (composite morbidity: one or more of death, chronic lung disease, or major cerebral abnormality on ultrasonography, 12.7% versus 15.2%, $P = .08$) with erythromycin therapy [42]. Oral amoxicillin–clavulanic acid prolonged pregnancy (43.3% versus 36.7% undelivered after 7 days, $P = .005$) and reduced the need for supplemental oxygen (30.1% versus 35.6%, $P = .05$), but was associated with an increased risk of necrotizing enterocolitis (1.9% versus 0.5%, $P = .001$) without reducing other neonatal complications. The combination of oral amoxicillin–clavulanic acid and erythromycin yielded similar findings. Although oral erythromycin was effective in reducing infant complications, many need to be treated with oral erythromycin to pre-

vent one adverse outcome, given the relatively small differences in outcomes between groups.

The ORACLE trial has raised concern that amoxicillin–clavulanic acid might increase the risk of neonatal necrotizing enterocolitis. This finding is somewhat at odds with the NICHD-MFMU trial, which found a reduction in stage 2 to 3 necrotizing enterocolitis with aggressive antibiotic therapy in a higher-risk population. Overall, the most recent meta-analysis did not find an increased risk of necrotizing enterocolitis with antibiotics, but it is prudent to avoid amoxicillin–clavulanic acid, and also to reduce exposure to any broad-spectrum antibiotics (and chorioamnionitis) by delivering women with PROM near term expeditiously.

It has been questioned whether the duration of antibiotic therapy might be decreased to reduce the potential selection of resistant microorganisms [44,45]. The two prospective studies that have addressed this did not demonstrate increased neonatal risk with shorter duration therapy, and also did not demonstrate less effect on latency than more prolonged therapy. Alternatively, neither study had an adequate sample size and power to demonstrate equivalence between the studied regimens. As such, the NICHD-MFMU protocol of 7 days of therapy is currently recommended.

Because of the several possible indications for antibiotic treatment in this population, attention should be given to avoidance of duplicate treatments. Where possible, antibiotic treatment should include the least number of different antibiotics, in adequate dosages for the identified indications. For example, the patient with evident chorioamnionitis who is receiving intravenous ampicillin and gentamicin or the patient being treated with intravenous cephazolin intrapartum for a concurrent urinary tract infection, does not require additional group B streptococcus therapy with penicillin. The patient receiving ampicillin and erythromycin for pregnancy prolongation that is identified to also have *C trachomatis* should be treated with erythromycin in adequate dosage to be effective for both indications.

How should the patient with preterm premature rupture of the membranes and cerclage be managed?

Cervical cerclage, particularly emergent cerclage, is a common risk factor for PROM [9,46,47]. There are a number of retrospective studies but no prospective trials regarding the optimal management of PROM with a cervical cerclage in place. It has been found that the risk of adverse perinatal outcomes after PROM with a cerclage is similar to that seen when there is no cerclage in place if the stitch is removed on presentation [48,49]. Studies comparing cerclage retention versus removal after preterm PROM have been small [50–52]. Although these studies seem to have conflicting results, there are several consistent patterns. First, each has found insignificant trends toward increased maternal infection with retained cerclage, and one study found increased infant mortality and death

from sepsis with retained cerclage, despite brief pregnancy prolongation. Second, no controlled study has found a significant reduction in infant morbidity with cerclage retention after preterm PROM. Given potential risk without evident neonatal benefit, it is recommended that cerclage be removed on presentation with PROM, particularly if the history of cervical incompetence is equivocal. It may be appropriate to leave the stitch in place during antenatal corticosteroid administration, with removal at 24 to 48 hours, but the benefit of this approach has not been confirmed. If cerclage is retained under this circumstance it is prudent to give concurrent broad-spectrum antibiotics as described previously.

Should antenatal corticosteroids be given in the setting of preterm premature rupture of the membranes?

Antenatal corticosteroid administration should be considered concurrent to conservative management of preterm PROM. These patients are considered to be at significant risk for perinatal morbidity (otherwise they should be delivered). Two recent prospective trials of antenatal corticosteroids concurrent to antibiotic administration have found less RDS (18.4% versus 43.6%, $P = .03$) and no evident increase in perinatal infection (3% versus 5%, $P = $ NS) with antenatal corticosteroids after preterm PROM at 24 to 34 weeks [53], and less perinatal death with treatment for those remaining pregnant at least 24 hours after initiation of treatment (1.3% versus 8.3%, $P = .05$) without an apparent reduction in RDS [54]. The most recently published meta-analysis in this regard has found antenatal corticosteroids during conservative management of PROM to substantially reduce the risks of RDS (20% versus 35.4%), intraventricular hemorrhage (7.5% versus 15.9%), and necrotizing enterocolitis (0.8% versus 4.6%), without significantly increasing the risks of maternal (9.2% versus 5.1%) or neonatal (7% versus 6.6%) infection [55]. Antenatal corticosteroids, either a single course of betamethasone (12 mg intramuscularly, every 24 hours × 2 doses) or dexamethasone (6 mg intramuscularly, every 12 hours × 4 doses), should be administered during conservative management if they have not been previously given.

It has been suggested women with PROM would deliver too quickly to benefit from antenatal corticosteroid administration. This is clearly not the case, because most remain pregnant at least 48 hours, regardless of concurrent antibiotic administration. It has also been suggested that preterm PROM itself might accelerate fetal pulmonary maturation. This is controversial, and even if true, RDS remains the most common acute morbidity in this setting (41% in the NICHD-MFMU trial) [41]. Finally, it has been suggested that antenatal corticosteroid treatment might increase the risk of neonatal infection. This has not been confirmed in meta-analyses, and review of individual studies has revealed no consistent pattern toward increased or decreased infection. With antibiotic treatment, most conservatively managed women with preterm PROM remain pregnant for at least 24 to 48 hours and the risk of infection is decreased. It is prudent to give

concurrent broad-spectrum antibiotics as noted previously to prolong pregnancy and reduce infectious morbidity in this situation.

Should tocolytic therapy be used after preterm premature rupture of the membranes

Current data do not confirm that tocolytic therapy after preterm PROM reduces infant morbidity and mortality. Because of this, and because of the potential for intrauterine infection in this setting, some caregivers elect not to treat these women with tocolytic agents, and this is appropriate. Alternatively, prophylactic tocolysis after PROM, particularly if contracting (preterm labor) occurred before preterm PROM, has been found briefly to prolong latency. No studies have evaluated tocolysis given concurrently with antenatal corticosteroid and antibiotics administration. It is plausible that short-term pregnancy prolongation with prophylactic tocolysis could enhance the potential for corticosteroid effect and allow time for antibiotics to act against subclinical decidual infection. It is not unreasonable to administer tocolysis under such circumstances. Further study is needed.

Are neurologic complications linked to preterm premature rupture of the membranes?

Increasing evidence has linked intra-amniotic infections to long-term neurologic complications. Cerebral palsy and cystic periventricular leukomalacia have been linked to amnionitis [56]. Elevated amniotic fluid cytokines and fetal systemic inflammation (termed ''fetal inflammatory syndrome''), which may accompany maternal-fetal infection, have been associated with periventricular leukomalacia and subsequent cerebral palsy [57–59]. Because early delivery and perinatal infection are commonly seen with PROM, it might be suggested that women with PROM should be delivered regardless of gestational age. It has not been shown, however, that immediate delivery on admission prevents these sequelae. Although there may not be overt infection on presentation with PROM, it is possible that subclinical infection is already present in some cases and that early delivery does not help. Alternatively, for those with PROM remote from term, conservative management with concurrent antibiotic administration does offer the opportunity to reduce gestational age–dependent and infectious complications. Until evidence of the benefits of immediate delivery become available, conservative management with adjunctive antibiotics to reduce the risk of infection is recommended for women with PROM remote from term (<32 weeks). Near term (≥32 weeks), the risk of major acute and chronic morbidity with delivery is low if pulmonary maturity is documented. Antenatal corticosteroids

can be given to accelerate fetal maturation if pulmonary testing is unavailable or suggestive of immaturity. Early delivery should be considered for these women, to reduce the risk of exposure to intrauterine infection and subsequent neurologic morbidity.

Summary

When PROM occurs before term, there are a number of interventions to reduce perinatal complications. In general, unless there is an opportunity to reduce gestational age–dependent morbidity or mortality with conservative management through either antenatal corticosteroid administration or extended latency, the patient is best served by expeditious delivery before complications, such as chorioamnionitis, umbilical cord compression, or abruption occur. When conservative management is undertaken, timely antenatal transfer to a center with facilities for maternal observation and neonatal resuscitation or care, in-hospital monitoring to allow monitoring and early intervention for infection, labor, bleeding, and nonreassuring fetal heart rate patterns, antenatal corticosteroid administration to enhance pulmonary maturation and reduce intraventricular hemorrhage, antibiotic treatment to prolong pregnancy and reduce perinatal infections, and intrapartum group B streptococcus prophylaxis in the absence of recent negative anovaginal cultures each offer the opportunity to enhance pregnancy outcomes.

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