PRELABOR RUPTURE OF THE MEMBRANES

Roberto Romero[1,2,3], Lami Yeo[1,4], Francesca Gotsch[1], Eleazar Soto[1], Sonia S. Hassan[1,4], Juan Pedro Kusanovic[1] and Ray Bahado-Singh[4]

[1]Perinatology Research Branch, NICHD/NIH/DHHS, Detroit, Michigan, USA
[2]Center for Molecular Obstetrics and Genetics, Wayne State University, Detroit, Michigan, USA
[3]Department of Epidemiology, Michigan State University, East Lansing, Michigan, USA
[4]Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan, USA

This work is based on several previous chapters that were published before by the authors in other textbooks. This work has been modified and adapted for this textbook. The original chapters are referenced and contain a more extensive discussion of the subject. This chapter has a clinical emphasis. The work has been primarily done by Roberto Romero, who is a government employee, and therefore, this is not subject to copyright.

PRELABOR RUPTURE OF THE MEMBRANES

INTRODUCTION

Prelabor rupture of the membranes (PROM) is rupture of the chorioamniotic membranes before the onset of labor.[1] The "latency period" is the interval between PROM and the onset of labor. There is no agreement about the length of the interval between rupture of the membranes and the onset of labor required to diagnose PROM. This period of time has varied between 1 to 12 hours in the literature.[2-9] The consequences of PROM depend on the gestational age. Therefore, this condition has been classified as "preterm PROM" or "term PROM," depending upon whether the episode occurs prior to or after 37 weeks of gestation.[2-12] The term "previable PROM" has been applied to gestations in which this complication occurs before 23 weeks,[12] while "preterm PROM remote from term" refers to the time frame between viability to about 32 weeks, and "PROM near term" is that which occurs between 32 and 36 weeks.[12]

FREQUENCY, TIMING AND SITE OF MEMBRANE RUPTURE

Frequency: Term PROM occurs in approximately 10% of patients while the frequency of preterm PROM is 2% to 3.5%.[5;13-17] Preterm PROM accounts for 30% to 40% of preterm deliveries and, therefore, is a leading clinically identifiable cause of preterm birth and a major contributor to perinatal morbidity and mortality.[2;5;13;14;16-19] It has been estimated that in the United States, approximately 150,000 women are diagnosed with preterm PROM every year.[20]

Spontaneous Rupture of Membranes in Normal Pregnancy: Figure 1 shows the proportion of women with spontaneous rupture of membranes as a function of cervical

dilatation.[21] Most patients rupture the chorioamniotic membranes at the end of the first stage of labor, hence the rationale for defining PROM as rupture of membranes before the onset of labor. The site of rupture is generally located in the most dependent part of the uterine cavity in close proximity to the cervix.[22] After invasive procedures such as fetoscopy, rupture of membranes can occur away from the cervix. The frequency with which spontaneous rupture of membranes occurs away from the most dependent part of the uterus ("high leak") is unknown.

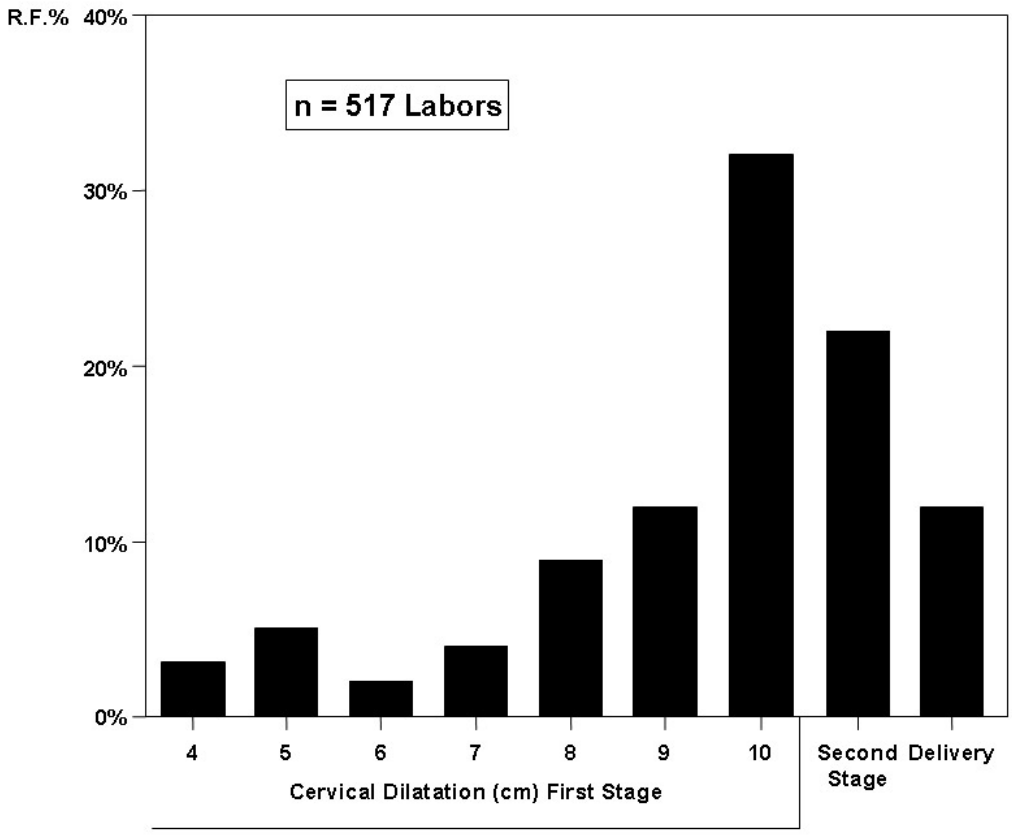

Figure 1

PRETERM PRELABOR RUPTURE OF MEMBRANES AS AN OBSTETRICAL SYNDROME

The current taxonomy of disease in obstetrics is largely based on the clinical presentation of the mother and not the mechanism responsible for disease. For example, the term "rupture of membranes" refers to a clinical condition in which amniotic fluid leaks from the amniotic cavity into the lower genital tract. However, the term ROM does not provide information about the cause (e.g. infection, a vascular insult, a weakness in the structure of the membranes, trauma caused by an invasive procedure (endoscopy), or other mechanisms of disease). We have proposed that the classification of disease in obstetrics is at a stage in which we recognize syndromes caused by multiple mechanisms of disease.[23] The features of these obstetrical syndromes are: 1) multiple etiologies; 2) long subclinical phase; 3) frequent fetal involvement; 4) adaptive clinical manifestations; and 5) predisposition due to gene-environment interaction.[24]

Preterm PROM is one of the "great obstetrical syndromes."[23] Multiple pathologic processes can lead to preterm PROM. The chronic nature of the pathologic process leading to preterm PROM can be inferred from the observations that women with a short cervix (≤ 25 mm) in the midtrimester,[25] a positive fetal fibronectin (FFN) in vaginal fluid,[25] bacterial vaginosis,[25] and bleeding in the first and second trimester of pregnancy[25-27] are at risk for the subsequent development of preterm PROM. Fetal involvement has been demonstrated, as 10% of all fetuses with preterm PROM have evidence of fetal bacteremia demonstrated by cordocentesis.[28] We have proposed that PROM is not the result of an accident, but rather a mechanism of host defense in the context of intrauterine infection (or other insults), and that spontaneous rupture of membranes occurs to facilitate the drainage of an infected cavity (intra-amniotic infection), as

well as to initiate labor (amniotomy is often followed by the onset of labor in term or preterm gestation). Therefore, rupture of membranes may be considered adaptive in nature. Other mechanisms of disease, such as chronic chorioamnionitis, in which there is infiltration of the chorion laeve with lymphocytes but no evidence of infection represents another potential mechanism for preterm PROM.[29] The underlying mechanism of disease appears to be immune in nature -- maternal rejection of the fetal allograft. Fetuses born to mothers whose placentas are affected with chronic chorioamnionitis have evidence of a fetal inflammatory response syndrome. We propose that the initiation of labor in these cases is the result of a combination of a fetal inflammatory response and the maternal damage of chorion laeve by the lymphocytes and natural killer cells, which are capable of inducing apoptosis of the trophoblast.[29] In this context, rupture of membranes and the initiation of labor may also be adaptive in nature because the fetus is in a hostile environment unrelated to infection.

Finally, there is evidence that genetic factors predispose to preterm PROM. Polymorphisms for genes coding for MMP-1,[30] MMP-9,[31] MMP-8,[32] and SERPINH1[33] in the fetus have been associated with spontaneous rupture of membranes in case-control studies. Environmental factors, such as bacterial vaginosis[25;34] or a proinflammatory vaginal milieu,[35] have also been associated with PROM. Evidence for a gene-environment interaction for preterm birth has been demonstrated between bacterial vaginosis and a polymorphism for the pro-inflammatory cytokine, TNF-α.[36;37] It is also possible that gene-gene interactions are operative. The genetic predisposition for preterm PROM is likely to result from the effect of multiple alleles, which individually confer a small risk for preterm PROM. Epigenetic changes in MMP-1 have been found to be associated with preterm PROM.[38] Collectively, the evidence reviewed

above supports the concept that preterm PROM is not a single condition, but one of the great obstetrical syndromes.

Mechanisms of Disease Implicated in Preterm PROM:

1. Intra-amniotic infection/inflammation: Preterm PROM is associated with positive amniotic fluid cultures for bacteria at the time of admission in approximately 30% of cases.[39] With the use of molecular techniques, about 50% of cases have microbial footprints in the amniotic cavity at the time of admission.[40] However, intraamniotic infection can be a primary cause of PROM or be a consequence of the rupture of membranes. There is evidence that infection precedes preterm PROM in a fraction of cases. In a study in which amniotic fluid cultures for microorganisms[41-43] and pro-inflammatory cytokines[44] were measured in the amniotic fluid of women undergoing mid-trimester amniocentesis, some women with positive cultures or elevated biomarkers of inflammation subsequently developed preterm PROM.[41-43]

2. Vascular pathology: In a study examining histologic lesions of the placenta, Arias et al. found that women who delivered with preterm PROM fell in general terms into two subgroups: those with acute histologic chorioamnionitis and another group with vascular lesions of the placenta.[45] Some patients have both types of lesions.[46] The vascular lesions observed include: "failure of physiologic transformation of the spiral arteries,"[47;48] atherosis, fibrinoid necrosis of the decidual vessels, and decidual vessel thrombosis consistent with decidual vasculopathy.[49] Vaginal bleeding during pregnancy is a risk factor for preterm PROM.[50] We have proposed that some patients who bleed in the first or second trimester of pregnancy have a disorder of decidual hemostasis.[50] Vaginal bleeding may predispose to membrane rupture by causing a separation between the chorioamnion and the decidua, which weakens the fetal membranes.[50] Alternatively, during the formation of a retroplacental clot, thrombin is generated.[51] This enzyme

can stimulate the production of MMP-1[52] and MMP-3[51] by decidual cells in culture media of chorioamniotic membranes.[53] These MMPs can degrade fibrillar collagen (types I and III) and other components of the extracellular matrix of the chorioamniotic membranes[54]. The mechanisms responsible for defective decidual hemostasis during pregnancy have not been identified. It is possible that vascular disease leading to microthrombosis in the decidua leads to local necrosis and bleeding. In some cases, vaginal bleeding will be the only clinical manifestation of intrauterine infection.[50] This association is important because women with preterm PROM often have clinical or sub-clinical abruptions, and histologic examination of the membranes indicates that acute chorioamnionitis is frequent in patients with abruption.[55]

3. Uterine cervical pathology: Women with surgery in the lower genital tract, such as cervical conization[56;57] or previous spontaneous abortions,[58] are at greater risk for preterm PROM. Buchmayer et al. reported that a history of two or more spontaneous abortions was associated with an odds ratio of 4.1 [95% CI: 2.2-7.8] for preterm PROM.[58] We propose that some degree of cervical insufficiency (e.g. a short cervix resulting in an inadequate mucus plug) predisposes to ascending intrauterine infection.[59;60] This hypothesis would explain the link between a short cervix and subsequent preterm PROM.[25] It is noteworthy that a cervical length $\leq$ 25 mm confers an increased risk for preterm PROM before 35 weeks of gestation in nulliparas (OR 9.9), as well as in multiparas (OR 4.2).[25]

4. Acquired or congenital connective tissue disorders: There is evidence that a connective tissue disorder, which can affect the membranes (the chorioamniotic membranes are fetal tissue), may predispose to preterm PROM. For example, patients with Ehler-Danlos syndrome are at increased risk for preterm PROM if they carry an affected fetus.[61] However, the attributable risk of Mendelian disorders for preterm PROM is extremely low. It is likely that a genetic

predisposition to preterm PROM can be due to the effect of multiple genes. Indeed, a relationship between polymorphisms in the promoter region of genes encoding for MMPs may also predispose to membrane rupture (MMP-1,[30] MMP-8,[32] MMP-9[31]) and SERPINH1.[33] polymorphisms may confer a mild to moderate risk, but this risk may be increased in patients who have a relative deficiency of vitamin C (environmental contribution).

CLINICAL RISK FACTORS FOR MEMBRANE RUPTURE

Harger et al. reported a comprehensive analysis of risk factors associated with preterm PROM in 341 women with preterm PROM (20 to 36 weeks) and 253 controls matched for maternal age, gestational age, parity, type of care (private vs. clinic), and previous vaginal or cesarean delivery.[62] Three factors associated with preterm PROM were identified: 1) previous preterm delivery; 2) vaginal bleeding during the index pregnancy; and 3) cigarette smoking. Similar findings have been reported in a case-control study of 138 patients with preterm PROM and 267 controls. Vaginal bleeding, smoking and low socioeconomic class were also found to be independent risk factors for preterm PROM.[63]

In a large, multicenter, observational cohort study, Mercer et al. reported the risk factors for preterm PROM (less than 35 weeks), stratified according to parity (see Table 1).[25] In conclusion, vaginal bleeding, a short cervix ($\leq$ 25mm), a history of previous spontaneous preterm delivery (with intact or ruptured membranes), and smoking are risk factors for preterm PROM in the index pregnancy. A history of preterm birth with preterm PROM in a previous pregnancy confers a high risk for recurrence (approximately 20%).[56]

CLINICAL CONSEQUENCES OF PREMATURE RUPTURE OF THE MEMBRANES

A. Preterm Parturition: Preterm PROM is followed by the onset of labor and delivery within a week in the majority of cases. The duration of the latency period is inversely related to the gestational age. The lower the gestational age, the longer the latency period.[64-66] Cox et al. described the natural history of preterm PROM in 298 patients managed expectantly without the use of steroids, tocolytics, and prophylactic antibiotics.[64] Of the 267 patients who gave birth to infants weighing ≥750 g, only 7% remained undelivered for more than 48 hours after admission.

Wilson and coworkers reported the outcome of 143 patients with preterm PROM managed expectantly; only 18% of patients remained undelivered after 1 week of admission.[65] Maternal febrile infectious morbidity (antepartum and postpartum) occurred in 10% of patients and the neonatal death rate was 13.1%.

The most comprehensive study of the natural history of preterm PROM was reported by Nelson et al., who evaluated the outcome following expectant management of 511 women with a singleton gestation and preterm PROM between 20-36 weeks.[66] Fifty-two percent of patients delivered within 48 hours, while 12.9% remained undelivered after 1 week. The perinatal death rate was 8.4%. Not surprisingly, most deaths occurred at gestational ages of less than 28 weeks [42.7%]. Maternal infection occurred in 21.7%, and the occurrence of fetal death was strongly associated with infection. The perinatal mortality was higher in neonates born to infected mothers with preterm PROM before 28 weeks, than after 28 weeks [46.6% vs. 1.2%], as was infection-related morbidity [36% vs. 19.8%].

B. Infection: Rupture of membranes is strongly associated with maternal or fetal infection. Maternal infection can be expressed as clinical chorioamnionitis. However, most women who have microbial invasion of the amniotic cavity (MIAC) do not have evidence of infection,[67] such as fever, leukocytosis, etc. Indeed, in our experience, only 20% of patients with preterm PROM and a positive amniotic fluid culture for bacteria have clinical evidence of chorioamnionitis.[68]

The prevalence of positive amniotic fluid cultures in women with preterm PROM is 32.4%[39], whereas in term PROM the prevalence is 34.3%.[69] However, this represents a minimum estimate of the frequency of infection, because the frequency is dependent upon isolation of microorganisms with standard microbiologic techniques, which underestimate the true rate of infection. The application of molecular microbiologic techniques (cultivation independent) has yielded a higher rate of microbial footprints (50%).[40] Patients who have a positive PCR result for microorganisms, but a negative culture, have comparable outcomes to those who have a positive amniotic fluid culture for microorganisms.[70]

Genital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*) are the most frequent isolates from the amniotic fluid, followed by *Streptococcus agalactiae*, *Fusobacterium* species, and *Gardnerella vaginalis*. Polymicrobial infection is found in 26.7% of cases[28;68;71-75] and an inoculum size greater than 10^5 colony-forming units per mL is found in 23% of patients.[75] The most common microorganisms isolated from women with term PROM are *U. urealyticum*, *Peptostreptococcus*, *Lactobacillus*, *Bacteroides* species, and *Fusobacterium*.[69]

Patients with intraamniotic infection are more likely to develop chorioamnionitis, endometritis, and neonatal sepsis than patients with negative amniotic fluid cultures on admission.[28;68;71-86] The frequency of respiratory distress syndrome (RDS) is two-fold higher in

neonates born to women with positive amniotic fluid cultures than those born to women with negative cultures.[80]

One study has examined the relationship between MIAC and the onset of preterm labor in women with PROM.[68] Patients in labor on admission had a higher rate of positive amniotic fluid cultures than women admitted with preterm PROM but not in labor [39% vs. 26%, p=0.049]. Moreover, 75% of patients who were not in labor on admission, but subsequently went into spontaneous labor, had a positive amniotic fluid culture around the time of the onset of labor.

Zlatnik et al. conducted a unique study in which the results of amniotic fluid culture were not used in patient management. A higher proportion of patients with positive amniotic fluid cultures delivered within 7 days, as compared to those with negative cultures [positive cultures: 89% vs. negative cultures: 45%, p=0.04)].[75] These data support a relationship between MIAC and the onset of preterm labor.

Can routine antibiotic administration eradicate intraamniotic infection and prevent secondary infection? A recent study investigated the course of MIAC in 46 patients with preterm PROM.[87] All underwent amniocentesis upon admission, with an 18% prevalence of intra-amniotic inflammation (defined as an amniotic fluid WBC count $\geq 100/mm^3$) and a 15% prevalence of MIAC. Patients without evidence of intra-amniotic inflammation or MIAC were treated with ampicillin and erythromycin for 7 days. Those with intra-amniotic inflammation or MIAC were treated with ceftriaxone, clindamycin, and erythromycin for 10-14 days. At the time of the second amniocentesis, six of the seven patients with a prior diagnosis of MIAC were again positive for microorganisms. Of 18 patients with intra-amniotic inflammation, only three showed no evidence of inflammation after antibiotic treatment. Of note, among patients with no evidence of intra-amniotic inflammation or MIAC at admission, 32% developed inflammation despite

therapy. Five of the nine patients in question had positive amniotic fluid cultures. These observations suggest that systemic treatment with these antibiotics may not alter the natural course of intraamniotic infection in preterm PROM.

Evidence that fetal infection (bacteremia) is frequently present in preterm PROM was provided by Carroll et al., who performed amniocentesis and cordocentesis at the time of presentation with PROM.[88] The frequency of positive fetal blood culture was 10.3%. The authors found that for patients with positive amniotic fluid and fetal blood cultures, the median time to delivery was 2 days [range: 1-5], compared with 41 days [range: 1-161] for patients with negative cultures in both amniotic fluid and fetal blood. In the case of patients with MIAC and negative fetal blood cultures, the median interval to delivery was 9 days [range: 1-37].[88]

The microorganisms isolated from septic newborns are similar to those found in the amniotic fluid. In a study of 221 patients with preterm PROM, six cases with culture-proven neonatal sepsis were found.[68] In five of these cases, the microorganisms were the same as those found in the amniotic fluid; in the remaining case, the amniotic fluid culture 48 hours before delivery had been negative.[68] The practical implication of this observation is that an amniocentesis performed before delivery may provide microbiological information helpful in guiding antibiotic choice in the newborn.

Fetuses with preterm PROM can mount a systemic inflammatory response.[89] The term "fetal inflammatory response syndrome" (FIRS) refers to an elevation in the fetal plasma concentration of IL-6 (> 11 pg/ml) that was associated with severe neonatal morbidity[89] and a shorter cordocentesis-to-delivery interval.[90]

Fetal microbial invasion or other insults result in a systemic inflammatory response that can progress toward multiple organ dysfunction, septic shock, and perhaps death in the absence

of timely delivery. Evidence of multisystemic involvement in cases of FIRS includes increased concentrations of fetal plasma MMP-9,[91] an enzyme involved in the digestion of type IV collagen and in the pathophysiology of preterm PROM.[92] Moreover, several fetal organs including the hematopoietic system,[93-95] adrenals,[96] heart,[97] brain,[98;99] lungs,[100;101] and skin[102] are target organs during FIRS.

Pathological examination of the umbilical cord is an easy approach to determine whether fetal inflammation was present before birth. Funisitis and chorionic vasculitis are the histopathologic hallmarks of FIRS.[103] Funisitis is associated with endothelial activation, a key mechanism in the development of organ damage,[104] and neonates with funisitis are at increased risk for neonatal sepsis[105] and long-term handicaps, such as bronchopulmonary dysplasia (BPD)[99] and cerebral palsy.[101] Indeed, newborns with funisitis are at more than a two-fold increased risk for intraventricular hemorrhage[106] and have an 11-fold risk for development of periventricular echolucencies.[107] In the context of FIRS, the combination of inflammatory changes in the brain and fetal systemic hypotension may increase the likelihood of brain injury.[108] Collectively, these observations suggest that a subset of fetuses presenting with preterm PROM have bacteremia and/or FIRS that may contribute to fetal organ damage.

The traditional view has been that MIAC is the consequence of membrane rupture. However, evidence suggests that PROM may be the result of sub-clinical infection and inflammation. Naeye and Peters reported in 1980 that patients with preterm PROM 1 to 4 hours before the onset of labor had a higher prevalence of histologic chorioamnionitis than patients who delivered preterm without PROM.[109] Because it is unlikely that inflammation of the chorioamniotic membranes develops in 4 hours, these data suggest that in these cases histologic chorioamnionitis precedes rather than follows PROM. Several lines of evidence suggest that the

most likely cause of histologic chorioamnionitis is sub-clinical infection. Bacteria have been recovered from 72% of placentas with histologic chorioamnionitis.[110] Furthermore, we have demonstrated a good correlation between a positive amniotic fluid culture for microorganisms and histologic chorioamnionitis.[111]

MIAC can also be the consequence of PROM. The frequency of positive amniotic fluid cultures increases with time. Indeed, 75% of patients who were quiescent on admission and subsequently went into labor had a positive amniotic fluid culture.[68] Only 25% of these patients, however, had a positive culture on admission, and the remaining 50% became positive during the latency period.[68] These observations are consistent with those of Naeye and Peters, who showed that the incidence of histologic chorioamnionitis increases with the duration of the latency period.[109]

The authors reported that histologic chorioamnionitis (defined as the presence of 4 to 15 neutrophils in the chorionic plate) in PROM was two- to three-fold more common when rupture of membranes occurred just before the onset of labor than when it occurred after labor began.[109] This suggests that inflammation (and probably infection) is in many cases not only a consequence of PROM, but also its cause.

C. Abruptio Placentae: Abruptio placentae occurs more frequently in patients with preterm PROM than in those with preterm labor and intact membranes [2.29% vs. 0.86%, respectively, RR: 3.58, 95% CI: 1.74-7.39].[112] The same conclusion was reported in a systematic review[113] and a population-based epidemiologic study.[114] Nelson et al. proposed that leakage of fluid after PROM may lead to a disproportion between the placental and uterine surfaces that would favor placental separation.[115] In the context of preterm PROM, the incidence of abruptio placentae increases with the severity of oligohydramnios (12.3% for patients with a vertical pocket of 1-2

cm vs. 3.5% among those with a vertical pocket > 2 cm).[116] However, two groups of investigators using subjective means to estimate amniotic fluid volume could not confirm this observation.[117;118]

An alternative hypothesis to explain the relationship between abruptio placentae and preterm PROM postulates that a disorder of decidual hemostasis leads to separation of the membranes from the decidua, with subsequent compromise of their nutritive support, weakening of the membranes, and eventual rupture. Indeed, patients with abruptio placentae after preterm PROM have a higher incidence of vaginal bleeding before rupture and during the latency period than patients without abruptio placentae.

Infection/inflammation within the decidua could also facilitate premature placental detachment. Indeed, there is an association between histologic chorioamnionitis and abruptio placentae.[55;119] The relative risk for abruption is 9.03 [95% CI: 2.80-29.15] when chorioamnionitis is associated with preterm PROM.[112]

D. Pulmonary Hypoplasia: The frequency of pulmonary hypoplasia is related to gestational age at the time of membrane rupture, and its presence increases the risk of neonatal death and other complications such as pneumothorax and persistent pulmonary hypertension.

Three studies examined the frequency of pulmonary hypoplasia in the context of preterm PROM. Vergani et al. conducted a prospective study of patients with PROM before 28 weeks of gestation managed conservatively and found that the frequency of pulmonary hypoplasia was 28%.[120] Gestational age at the time of PROM and presence of oligohydramnios, but not the latency period, were independent predictors of pulmonary hypoplasia.[120]

Rotschild et al. studied 88 neonates born to mothers with PROM occurring before 29 weeks and a latency period of at least one week.[121] The prevalence of pulmonary hypoplasia was

16%. Gestational age at the time of PROM, but not the duration of the latency period or the severity of oligohydramnios, was associated with pulmonary hypoplasia. The risk of pulmonary hypoplasia when PROM occurs at 19 weeks was 50%, whereas it was only 10% when the membranes ruptured at 25 weeks.

Winn et al. prospectively studied 163 patients with preterm PROM from 15 to 28 weeks of gestation.[122] The incidence of pulmonary hypoplasia was 12.9%. The authors reported that gestational age at rupture of the membranes, latency period, and either the initial or the average amniotic fluid index (AFI) had significant influence on the development of pulmonary hypoplasia.

The role of duration of rupture of membranes in the development of pulmonary hypoplasia is not clear. Univariate analysis demonstrated an association between the duration of rupture of membranes and the occurrence of pulmonary hypoplasia.[120;123-125] However, there is an inverse relationship between the duration of the latency period and the gestational age at the time of membrane rupture. Multivariate analysis has not shown a significant effect of the duration of PROM in the development of pulmonary hypoplasia.[120]

Whereas Rotschild et al.[121] reported that the severity of oligohydramnios was not a factor in the development of pulmonary hypoplasia, both Vergani et al.[120] and Winn et al.[122] reported that amniotic fluid volume was an independent predictor of the development of pulmonary hypoplasia. The discrepancy between studies may be explained by the: 1) determination of amniotic fluid volume; 2) exclusion of patients; and 3) definition of pulmonary hypoplasia.

E. Fetal Compression Syndrome: The fetal compression syndrome was originally described in the context of oligohydramnios and renal agenesis.[126] Classically, it includes limb position deformities and craniofacial defects that are thought to result from physical compression

inhibiting fetal growth and movement.[127;128] Nimrod et al. reported an incidence of 12% in women with preterm PROM, most occurring when the latency period was longer than 5 weeks.[124] Blott and Greenough found that 46% of infants born after prolonged membrane rupture (more than 4 weeks) had limb deformities.[129] The median duration of rupture in the group with deformities was 28 days, compared with 9 days in infants without deformities.

F. Fetal Growth Restriction: Preterm delivery resulting from patients with preterm labor and intact membranes or preterm PROM has been associated with "fetal growth restriction". Most studies are cross-sectional and have not separated preterm PROM from preterm labor with intact membranes.[130;131] One interesting study determined the fetal growth rate for biometric parameters in a cohort of 69 singleton pregnancies complicated with preterm PROM (24-31 weeks) and who remained undelivered for more than 14 days. The mean growth velocity of the head and abdominal circumference was significantly lower than that of the control group [n=345 normal pregnancies]. Neonates who had either IVH, PVL or cerebral palsy had a lower growth velocity than those not affected with these disorders.[132]

G. Fetal Death: The rate of fetal death in preterm PROM is approximately 1% when this complication is diagnosed after 24 weeks and 15% if PROM occurs before.[20] The etiology for fetal death remains unknown. Fetal infection, placental abruption, fetal growth restriction, umbilical cord proplase or accident (resulting from compression in cases of severe oligohydramnios) have been implicated.

Fetal death, in the context of intrauterine infection, has been attributed to microbial invasion of the fetus, where the unborn child fails to deploy an inflammatory response, which is sufficienly intense to stimulate labor. Indeed, the frequency of histologic chorioamnionitis (maternal inflammatory response) is 9 times more frequent than funisitis (a fetal inflammatory

response) in patients with stillbirth.[133] In this case, in utero fetal death would represent failure of the host response mechanisms dealing with intrauterine infection. This concept is supported by a genetic association study which demonstrated that fetal carriage of the allele 2 of the gene encoding for the IL-1 receptor antagonist (IL-1ra) is associated with fetal death.[134] An excess of IL-1ra in the fetal compartment may limit the ability of the fetus to deploy a pro-inflammatory response and limit the effectiveness of the mechanisms available for host defense, including the ability to initiate labor to exit a hostile intrauterine environment.

DIAGNOSIS

Presenting Symptoms: The most common presentation of PROM is a watery vaginal discharge or a sudden gush of fluid from the vagina, as reported by the patient. Obtaining information about the timing of the initial loss of vaginal fluid, color and consistency of the discharge, and any odor may help to differentiate PROM from loss of the mucus plug in early labor, vaginal discharge associated with infection, normal leukorrhea of pregnancy, and urinary incontinence (sometimes present in pregnancy), as well as to determine the presence of blood or meconium in the amniotic fluid.

Vaginal Examination: Evaluation of the patient begins with a sterile speculum examination. Visualization of a vaginal pool or obvious leakage of fluid from the cervix into the posterior fornix is considered evidence that PROM has occurred. Increasing intra-abdominal pressure may assist in the visualization of this sign. If no fluid is present in the posterior fornix, the patient can be re-examined after resting in the supine position to allow for accumulation of fluid in the posterior fornix. Additionally, a speculum examination allows for collection of vaginal and

cervical cultures and amniotic fluid to assess fetal lung maturity, as well as to rule out cord prolapse.

A sterile swab of fluid should be obtained from the posterior fornix and placed on a clean glass slide and on a piece of nitrazine paper. Amniotic fluid, when put on a slide and allowed to dry, will show arborization ("ferning") under the microscope at low magnification.[135] This method has an overall accuracy of 95%.[136] Rare false-positive ferning results have been described in association with fingerprints on the slide or contamination with semen and cervical mucus.[137;138] False-negatives (5-10%) may be caused by dry swabs or by contamination with blood.[135;139;140] The slide should be evaluated after at least 10 minutes of drying to decrease the false-negative rate.[141]

Should a digital examination of the cervix be performed in patients with preterm PROM? The traditional view has been that "once an examination has been performed, the clock of infection starts to tick". Adoni and coworkers reported a study in which the latency period and incidence of chorioamnionitis were evaluated in patients with preterm PROM (26-34 weeks) who underwent a digital examination or a sterile speculum examination.[142] The latency period was longer in patients undergoing speculum examination than in those digitally examined [9.5 days ± 1.5 vs. 3.1 days ± 0.5, $p<.005$]. No significant difference in the incidence of chorioamnionitis was found. Lewis and associates prospectively collected data on 271 singleton pregnancies with preterm PROM.[143] Patients who underwent a digital examination had shorter latency periods than those following speculum examination [digital examination: 2.1 days ± 4.0 vs. speculum examination: 11.3 days ± 13.4, $p<0.0001$].

Sukcharoen et al. performed a retrospective study in which women with preterm PROM had digital examinations or speculum examinations. The authors reported no differences in

latency periods or neonatal outcomes in the study groups. However, patients that underwent digital examinations had a higher frequency of chorioamnionitis [digital exam: 12% vs. speculum exam: 3.1%, $p<0.05$].[144]

Schutte and colleagues retrospectively examined the incidence of neonatal infection in patients with PROM according to the interval between initial digital vaginal examination and delivery.[145] The incidence of neonatal infection was higher in patients examined more than 24 hours before delivery than in those whose first vaginal examination occurred less than 24 hours before delivery [33% vs. 5%, $p<0.0001$].

The only justification for performing a digital examination is to determine cervical status. In the preterm gestation this information rarely alters clinical management, but in the term gestation the cervical state may influence decisions regarding induction. There is a strong relationship between the results of sterile speculum examination and digital examination of the cervix. This was demonstrated in a study in which visual speculum and digital cervical examinations in women in labor were performed by two separate blinded examiners within 5 minutes of each other. Visual examination underestimated actual cervical dilation by only 0.6 cm [95% CI: 0.58-0.62].[146-148]

Biochemical Studies to Diagnose Rupture of Membranes: The biochemical properties of the amniotic fluid are the basis to distinguish it from other fluids that can be observed in the vagina (i.e., cervical secretions, urine and semen). The normal pH of the vagina is 4.5 to 5.5 during gestation, and that of the amniotic fluid is 7.0 to 7.5. Nitrazine paper turns from yellow to blue when exposed to any alkaline fluid (i.e., pH of 7.0 or more) and the use of nitrazine paper has been reported to have an accuracy of 93.3%[136] to determine the presence of amniotic fluid in the vagina. False-positive results range from 1% to 17% and can result from

alkaline urine, blood, semen, vaginal discharge in cases of bacterial vaginosis, or *Trichomonas* infection.[149] False negatives may occur in up to 10% of cases.

Additional biochemical tests for the diagnosis of PROM include diamine oxidase (DAO) activity,[150] prolactin levels,[151-153] alpha-fetoprotein (AFP; sensitivity: 94.5% and specificity: 95.4%),[151;154] and insulin-like growth factor-binding protein-1 (IGFB-1).[155] AFP has been reported to be better than prolactin and more practical than DAO assay with an overall accuracy of 98%.[156;157] IGFBP-1 determinations have a sensitivity of 74.4% and specificity of 92.6%.[155] Overall, the sensitivity, specificity, positive and negative predictive values of the different diagnostic tests presented today in comparison to the nitrazine test are good.[158-163]

The assay for fetal fibronectin (FFN) is useful in the identification of patients at risk for preterm and term labor and imminent delivery. However, doubts still exist about its diagnostic value in PROM.[164] Eriksen reported that for the detection of term PROM, FFN had a sensitivity of 98.2%, but a specificity of only 26.8%.[165] Although the authors proposed that the false-positives were the result of the detection of small amounts of amniotic fluid not detected by clinical tests (pool, Nitrazine, and ferning), an alternative explanation is that a positive FFN detects degradation of the extracellular matrix in the fetal-maternal interface that precedes the clinical onset of labor rather than PROM. Support for the hypothesis derives from the observation that patients without PROM but with positive cervical FFN are more likely to deliver within 72 hours than those with negative cervical FFN.[164;166-173] In conclusion, the detection of cervicovaginal FFN is not specific for PROM.

Transabdominal injection of dye: When the diagnosis of preterm PROM is not clear, a transabdominal injection of dye (indigo carmine, Evans blue, fluorescein) into the amniotic cavity may be used for confirmation.[174-177] Methylene blue should not be used as it may cause

fetal methemoglobinemia.[178-180] A tampon in the vagina can document subsequent dye leakage in cases of PROM.

INITIAL ASSESSMENT

The initial evaluation of a patient with preterm PROM includes: 1) accurate assessment of gestational age; 2) estimation of fetal weight and presentation; 3) evaluation of the risk of infection; 4) determination of lung maturity; 5) assessment of fetal well-being; and 6) exclusion of occult cord prolapse.

1. Ultrasound Examination in the Evaluation of Patients with Preterm PROM: The initial ultrasound examination aims to: 1) assess fetal viability, biometry and presentation; 2) quantify amniotic fluid volume; 3) rule out fetal anomalies; and 4) confirm gestational age. The sonographic examination of fetuses with PROM may be challenging due to the reduced amniotic fluid volume. For example sonographic estimates of fetal weight have been shown to underestimate the birthweight.[181-183]

2. Diagnosis of Intrauterine Infection in Preterm PROM: Amniocentesis can be used for the evaluation of the microbiological state of the amniotic cavity and of fetal lung maturity in the patient with preterm PROM.[184] Results of amniotic fluid analysis provide a rational approach to the management of preterm PROM. Patients without evidence of infection/inflammation and lung immaturity could be managed expectantly while those with evidence of infection could be managed using algorithms tailored to the gestational age (see management section).

One randomized clinical trial examined the value of amniocentesis in preterm PROM.[185] Forty-seven patients (26 to 34 weeks of gestation with an accessible amniotic fluid pocket) were

randomized to amniocentesis or no amniocentesis. Indications for induction of labor included positive Gram stain of amniotic fluid or mature fetal lungs, as determined by a lecithin-to-sphingomyelin (L/S) ratio of more than 2.0 or positive phosphatidylglcerol (PG). Neonates born to women who had amniocenteses had a lower incidence of "fetal stress" during labor (diagnosed by fetal heart rate tracing) and a shorter hospital stay than those born to women who were randomized to not have amniocenteses ["fetal distress": 4% vs. 32%, $p<0.05$; hospital stay (median): 8.5 days vs. 22 days, $p<0.01$]. No differences in the rate of neonatal sepsis, maternal chorioamnionitis, or endometritis were noted between the two groups. This study had limited power to detect differences in neonatal morbidity.

The analyses of amniotic fluid used to detect the presence of MIAC or intra-amniotic inflammation include: 1) Gram stain; 2) a quantitative white blood cell (WBC) count; 3) glucose concentration; and 4) microbial cultures for aerobic, anaerobic bacteria, as well as genital mycoplasmas. Patients with a negative Gram stain (read by experienced personnel) and a high WBC count (more than 30 cells per uL) are at a high risk of having microbial invasion with genital mycoplasmas, which are not visible on Gram stain examination. Lower concentrations of glucose in amniotic fluid (<10 mg/dL) can serve as an additional marker for MIAC. The results of amniotic fluid culture may take days to be available. Therefore, most centers rely on the determination of intra-amniotic inflammation because the outcome of preterm PROM in patients with intra-amniotic inflammation is similar to those with MIAC proven with standard microbiological techniques.[186] Table 2 summarizes the diagnostic criteria and predictive values of different amniotic fluid tests in detecting positive amniotic fluid cultures in patients with preterm PROM.[85;187] Amniotic fluid IL-6 performed best in detecting MIAC, as well as in identifying patients at risk for impending preterm delivery and neonatal complications. We have

shown that amniotic fluid IL-6 is a sensitive test for the prospective diagnosis of acute histologic chorioamnionitis [IL-6 of more than 17 ng per mL had a sensitivity of 79% and specificity of 100%], significant neonatal morbidity (sepsis, RDS, pneumonia, intraventricular hemorrhage, bronchopulmonary dysplasia, and necrotizing enterocolitis), and mortality [IL-6 of more than 17 ng per mL had a sensitivity of 69% and a specificity of 79%].[188] Other rapid tests reported for the detection of MIAC include amniotic fluid catalase,[79] alpha$_1$-antitrypsin,[84] limulus amebocyte lysate test,[83] and bacterial polymerase chain reaction.[189]

A rapid bedside test for the detection of MMP-8 in amniotic fluid has been developed. This kit has been reported to have high accuracy in the identification of patients with MIAC and inflammation among patients with preterm labor and intact membranes.[190] Future studies may determine the utility of this test in the identification of patients with intra-amniotic infection/inflammation among patients with preterm PROM.

The risk of amniocentesis, when performed by experienced individuals, appears to be extremely low. Yeast and colleagues specifically addressed this issue in 91 patients with preterm PROM in whom amniocenteses were performed.[191] A retrospective review of neonatal records uncovered no evidence of fetal trauma with any procedure. This study also found that the incidence of spontaneous labor in patients who underwent amniocentesis was no different from that of patients who did not undergo amniocentesis secondary to oligohydramnios or an anterior placenta. The authors concluded that their study failed to show that amniocentesis might induce labor.

Assessment of Lung Maturity: Lung maturity can be assessed from the amniotic fluid obtained by amniocentesis or from the vaginal pool. The latter has the advantage of being less invasive and more feasible in patients with oligohydramnios. Amniotic fluid from the vaginal

pool can be collected in three ways: (a) from the posterior vaginal fornix by sterile speculum examination; (b) in a clean bedpan maintained under the patient; or (c) by use of obstetric perineal pads left in place for 12 to 24 hours to ensure saturation.[192-195] The success rate in obtaining fluid within 48 hours with these noninvasive techniques ranges from 54% to 100%.[194;195] Using a pad to detect phosphatydylglycerol (PG), Esol et al. found a sensitivity of 88%, specificity of 76%, positive predictive value of 34%, and negative predictive value of 98%.[196] Lewis et al. investigated the value of a rapid antibody agglutination method (Amniostat FLM) to detect PG in vaginal pool samples.[197] Thirty-six of 201 patients between 26 and 36 weeks of gestation had positive PG, and none of the infants born to these mothers developed RDS. PG was detectable only after 30 weeks of gestation.

The reliability of lung maturity tests from amniotic fluid collected vaginally has been challenged.[198;199] This section reviews the correlation between the lecithin/sphingomyelin (L/S) ratio and PG results in amniotic fluid obtained by amniocentesis and from the vaginal pool. Shaver and associates compared the phospholipid profile of paired amniotic fluid samples in 28 patients with preterm PROM.[192] No significant difference was found in the concentrations of PG, phosphatidylinositol, phosphatidylethanolamine, and phosphatidylserine in amniotic fluid obtained by the two sampling methods. The L/S ratio was higher in fluid collected transvaginally than in fluid collected transabdominally, but this difference did not reach statistical significance. The only phospholipid clearly increased by vaginal contamination was lysolecithin.

Dombroski et al. reported a study in which amniotic fluid was obtained by amniocentesis in patients at term in labor.[200] Thirty minutes after artificial rupture of membranes, a vaginal sample of amniotic fluid was collected. L/S ratios obtained from amniotic fluid in the vaginal

pool samples were significantly lower than were those obtained by amniocentesis. However, in 22% of cases, L/S ratios were higher in the vaginal pool samples than in amniocentesis.

Several studies have examined the value of PG determinations in amniotic fluid obtained transvaginally. Stedman et al. reported that of 25 patients with PROM between 26 and 34 weeks, 60% had positive PG and none of their neonates developed RDS (within 72 hours of the test).[193] Among the newborns of the 10 patients with negative PG, four developed RDS. Similarly, Brame and MacKenna reported no cases of neonatal RDS in 36 patients with PG found in vaginal fluid.[194]

The possibility that bacterial contamination from vaginal secretions may lead to false-positive PG results has been raised by Schumacher and associates, who reported that one patient had PG detected in the fluid from the vaginal pool, but not in fluid retrieved by transabdominal amniocentesis.[199] The neonate developed respiratory insufficiency that was attributed to either RDS or pneumonia (the amniotic fluid culture was positive for bacteria). These investigators also demonstrated that bacteria might be a source of PG. Therefore, excessive bacterial contamination may alter results of PG determinations. It would seem prudent to minimize the interval between sample collection and assay in the hope of preventing bacterial growth in the sample.

Three studies have reported neonatal outcome and L/S ratio results in preterm PROM.[194;195;201] In two of the studies, a mature L/S ratio was an indication for delivery.[195;201] In the third study, the presence of PG was used as an indication for delivery.[194] The data are consistent: with a mature L/S ratio, the risk of RDS is small. An L/S ratio of more than two was found in 103 patients, and none of the neonates developed RDS.

The available evidence indicates that fetal lung maturity studies can be performed on amniotic fluid obtained from the vagina, and that a mature L/S ratio or the presence of PG is associated with a very low risk of RDS. Moreover, this noninvasive, low-risk approach allows for serial L/S and PG determinations.

A mature phospholipid test has been demonstrated in approximately 50% of patients with preterm PROM at gestational ages of less than 34 weeks.[72;74;185] Garite and associates reported that none of the neonates with an L/S ratio of 1.8 or greater developed RDS.[74] The incidence of this complication in neonates with an immature L/S was 33%.

Two randomized clinical trials have examined the outcome of induction of labor in patients with a mature results. In the first trial, 47 patients with preterm PROM (less than 36 gestational weeks) and mature amniotic fluid indices were randomized to either prompt delivery or expectant management.[202] A mature test was defined as an L/S ratio above 2 or a Foam Stability Index (FSI) of 47 or more (often from vaginal fluid). There was no difference in perinatal mortality between the two groups. There were no cases of RDS in the expectant management group, but two in the prompt delivery group. One newborn died from severe hyaline membrane disease (birth weight 900 g, vaginal FSI=48), and the other neonate survived (birth weight 1,700 g, vaginal L/S=2.0). There were no differences in the rate of neonatal sepsis or other neonatal complications in the two groups. However, the only two cases of intracranial hemorrhage occurred in the prompt delivery group. Maternal chorioamnionitis was more common in the expectantly managed group than in the delivery group [38% vs. 8%, $p < 0.02$].

Mercer et al. reported the results of a randomized clinical trial in which 93 women with mature amniotic fluid phospholipid studies (vaginal or transabdominal amniocentesis FSI $\geq$ 47) were randomized to induction of labor with oxytocin or expectant management (bed rest).[203]

Maternal chorioamnionitis was more frequent in the expectant group. However, this difference did not reach significance. There were no significant differences in the cesarean delivery rate or in the incidence of confirmed neonatal sepsis between the groups. Suspected sepsis was higher in neonates born to women in the expectant group, as was antibiotic administration and septic workups. However, neonatologists were not blinded to treatment allocation.

ASSESSMENT OF FETAL WELL-BEING: The goal of fetal evaluation is to identify fetal infection/inflammation or a pathologic process, which increase the risk of antepartum or neonatal death. Methods of fetal surveillance include non-stress test and the components of the biophysical profile.

Nonstress Test (NST): The differential diagnosis of a non-reactive NST is 1) preterm gestation; 2) infection; and 3) hypoxia. The interpretation and the significance and management of fetal heart rate decelerations associated with umbilical cord compression due to oligohydramnios is also a challange.

Fetuses with preterm PROM between 24 and 37 weeks have a significantly higher incidence of reactive tracings than gestational age-matched counterparts with intact membranes.[204-206] This has been attributed to "accelerated fetal central nervous system maturation" and umbilical vein compression with resulting fetal heart rate accelerations.[207] Thus, lack of reactivity should not be ascribed to preterm gestation without further investigation.

A non-reactive NST is frequently observed in fetuses with MIAC. Three studies[208-210] have found the NST to be an insensitive predictor of infection-related outcome. A major issue is the high false positive rate (approximately 35%) of the NST for the detection of infection. Therefore, a non-reactive NST is not sufficient to diagnose infection. Evaluation of other

biophysical parameters and the results of amniocentesis are recommended before delivery can be indicated (see below).

Assessment of Amniotic Fluid Volume:

Contrary to what is generally believed, rupture of membranes is not necessarily associated with oligohydramnios. Harding et al. noted that the amniotic fluid index (AFI) in patients with preterm PROM remains stable after the membranes rupture, with the mean AFI on admission being 5.9 ± 2.5 cm and on the day of delivery 5.4 ± 2.0 cm.[211] Moreover, Vintzileos et al. reported that 65.5% of patients with PROM had a vertical pocket of amniotic fluid of greater than 2 cm, while 15.5% had a vertical pocket between 1 and 2 cm. Only 19% had a vertical pocket of less than 1 cm.[212]

Several studies have examined the relationship between oligohydramnios and outcomes in PROM. Patients with a vertical amniotic fluid pocket <1 cm have a shorter latency period and a higher incidence of chorioamnionitis and neonatal sepsis than patients with a vertical pocket greater than 2 cm.[212] Similar findings were reported by Gonik et al.[213] Women with a vertical amniotic fluid pocket of <1 cm had a higher incidence of chorioamnionitis and endometritis than those with an amniotic fluid pocket of >1 cm. No difference in the duration of the latency period between the two groups was found.[213]

Hadi et al. reported that chorioamnionitis occurred in 26.4% of women with an amniotic fluid pocket of less than 2 cm.[214] Similarly, Lao et al.[215] used a cutoff of 2 cm as the largest pocket of amniotic fluid to define oligohydramnios, and found that the frequency of chorioamnionitis and funisitis was higher in patients with oligohydramnios than in those without reduced amniotic fluid volume [chorioamnionitis: 55.3% vs. 29.3%; funisitis: 44.7% vs. 16.7%]. A reduction in amniotic fluid volume was also associated with MIAC.

There is an association between reduced amniotic fluid volume and maternal or neonatal infection-related morbidity and MIAC. The reason for the high rate of infection in patients with oligohydramnios is unknown. Intra-amniotic infection may alter amniotic fluid dynamics, leading to a reduction in fluid volume. Yoon et al. proposed that redistribution of blood flow away from the kidneys might take place as part of the host response to microbial products, and this may lead to olygohydramnios.[216]

Patients with decelerations have a lower AFI than those without decelerations [4.32 cm ± 1.67 vs. 6.47 cm ± 3.59, $p<0.01$].[217] This observation suggests that cord compression due to oligohydramnios may be the mechanism behind variable decelerations observed in patients with PROM.

Preterm PROM is associated with a significant and prolonged reduction of fetal breathing movements lasting approximately 2 weeks.[218;219] This phenomenon seems to be related to rupture of membranes per se, rather than to infection, hypoxia, or intrauterine growth restriction, even though the precise mechanisms are unknown. Membrane rupture leads to a reduction in intra-amniotic pressure and, thus, favors loss of lung fluid. Teleologically, a reduction in fetal breathing may be a mechanism to protect against lung fluid loss and pulmonary hypoplasia.

Vintzileos was the first to document an association between infection and decreased fetal breathing activity in preterm PROM.[220;221] Subsequently, we confirmed these findings and documented that women with positive amniotic fluid cultures had fewer and shorter episodes of fetal breathing activity than women with negative amniotic fluid cultures.[222]

The presence of fetal breathing has a very high negative predictive value (approximately 95%) for MIAC and neonatal sepsis. However, the absence of breathing activity has a limited positive predictive value (approximately 50%) for either of these two outcomes and, thus, it

cannot be used as an indication for delivery. Therefore, the presence of breathing indicates that infection is unlikely.

Intra-amniotic infection is associated with a dramatic reduction in fetal body movements.[222] Decreased fetal motion in the context of infection may be the counterpart of the reduction in motor behavior observed during the course of febrile illnesses in adults and children.

The biophysical profile (BPP) has been found to be helpful in the management of patients with PROM.[204;207-210;220;222-227] Vintzileos et al., using logistic regression analysis, demonstrated that each component of the BPP contains useful information for the prediction of infection-related morbidity (defined as maternal chorioamnionitis, possible neonatal sepsis, and proven neonatal sepsis). In their first study, a modified BPP scoring system that incorporated placental grading (with a maximal score of 12) was used.[220] A BPP score of seven or less was much better than any single component of the BPP in the prediction of infection-related outcome. Placental grading was the only parameter that had no predictive value. Thus, it was excluded from subsequent studies. The diagnostic indices of a BPP score $\leq$ 7 (performed 24 hours before delivery) were: sensitivity 94%, specificity 97%, positive predictive value 95%, and negative predictive value 97% in a population with a prevalence of infection-related outcome of 30%. This study was observational in nature and, thus, the BPP was not used for patient management.

Subsequently, Vintzileos et al. compared the outcome of pregnancy in patients managed with serial BPPs with two historical control groups: 1) expectant management without BPP or amniocentesis; and 2) management with a single amniocentesis on admission.[228] A BPP score $\leq$ 7 on two examinations two hours apart was used as an indication for delivery. An abnormal score required a non-reactive NST and absence of fetal breathing. The results of this study indicated that patients managed with daily BPPs had a lower rate of overall neonatal sepsis

(suspected and culture-proven) than patients in either control group. This study did not provide the frequency of other indices of neonatal morbidity (e.g., RDS, IVH, duration of mechanical ventilation) in the different groups. This issue is important, since 14 patients who were delivered because of a low BPP score showed no evidence of neonatal infection and, thus, could be considered false positives. If intervention was not associated with an increased rate of other neonatal complications, management with serial BPPs would seem a reasonable approach. The investigators found that the BPP had limitations when the interval between the test and delivery was longer than 24 hours, and that maternal infection without fetal infection was not correlated with the results of the BPP scoring. Vintzileos et al. subsequently reported on 111 fetuses with preterm PROM followed with daily BPPs, and found that as more of the biophysical activities became compromised, the higher the incidence of infection-related complications.[207]

It is noteworthy that subsequent to this work, three studies[223;224;227] reported an association between the results of the BPP and infection-related outcomes and three others could not confirm such an association.[225;226] Our explanation for the apparent discrepancy is that studies reporting negative results used the BPP at less-frequent testing intervals (48- to 72-hour intervals) than the daily testing used in positive reports.

MANAGEMENT OF PATIENTS WITH PREMATURE PROM

The management of patients with premature PROM depends on the gestational age at the time of membrane rupture (see Figure 2).

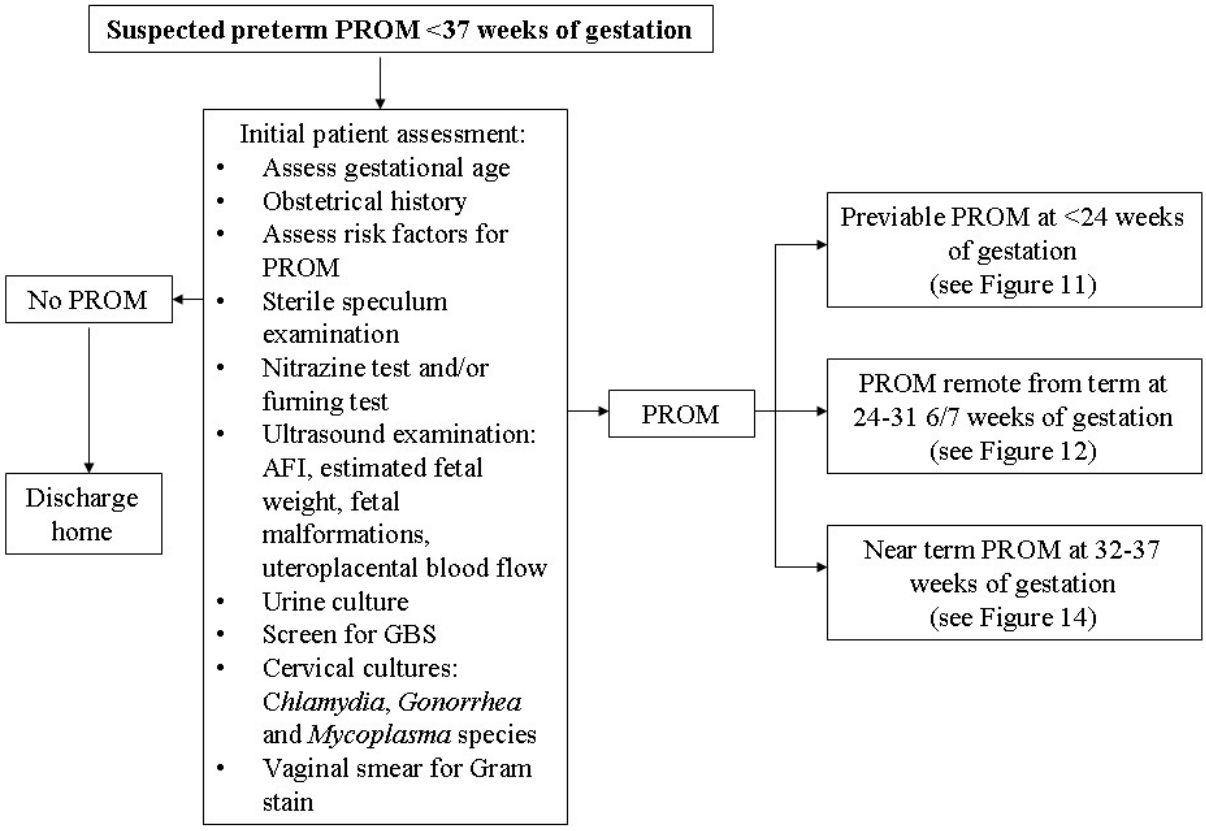

Figure 2

Previable PROM (see Figure 3)**:** The major complications of previable PROM are maternal infection, late abortion/preterm labor, low neonatal survival and a high risk of neurologic handicap.[229;230] Patients are generally offered two options: induction of labor or expectant management. The presence of intra-amniotic inflammation/infection in amniotic fluid analysis carries a poor prognosis because of the risk of spontaneous preterm labor as well as fetal morbidity. Management of these patients requires an in-depth discussion involving the parents, neonatologists and obstetricians and careful documentation in the medical record. The value of antibiotic or corticosteroid administration in previable PROM has not been established. However, our practice is to administer antibiotics to the patient who desires expectant

management. A systematic review of previable PROM indicates that the quality of the evidence to support the management is not high.[231]

Leakage of amniotic fluid after second-trimester amniocentesis should be considered a separate entity from previable PROM. It occurs in 1.2% of patients and is usually transient in nature.[232] The risk of delayed PROM in these cases is no different from that in the general population.[233]

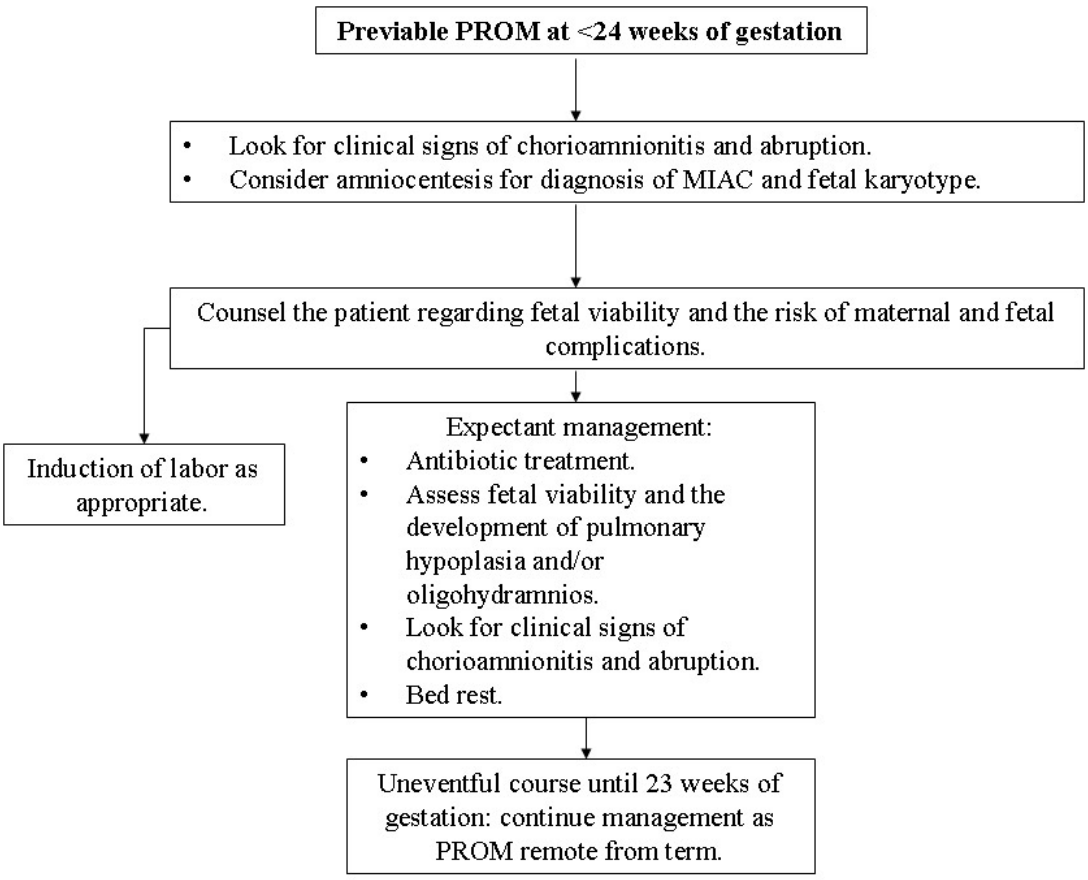

Figure 3

PROM Remote from Term (24-31 6/7 Weeks of Gestation) (see Figure 4): The management goals are to 1) exclude intra-amniotic infection/inflammation; and 2) institute expectant management in patients without documented infection/inflammation.

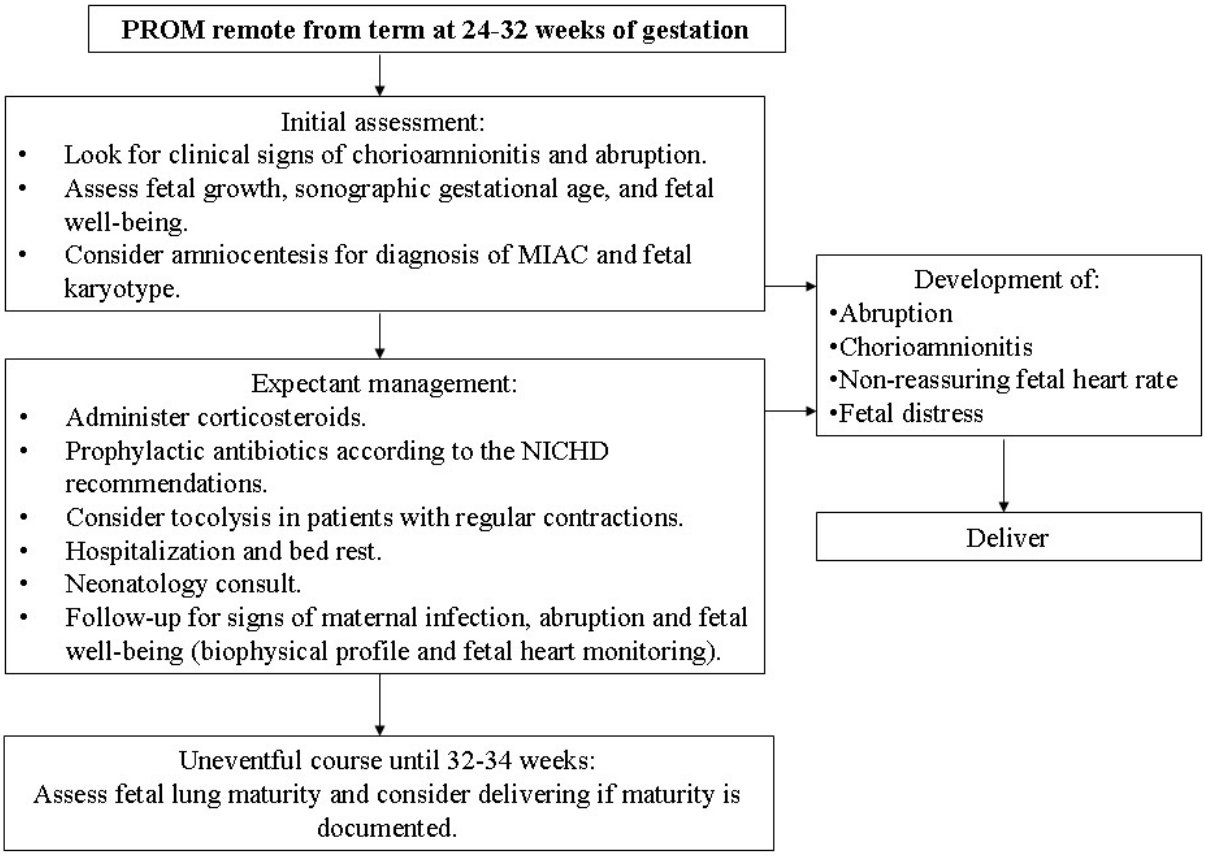

Figure 4

Intra-amniotic infection/inflammation and its management: The most accurate method for diagnosis of intra-amniotic infection/inflammation is amniocentesis. Once intra-amniotic infection/inflammation is identified in patients between 24-31 completed weeks of gestation, the optimal management is a challenge: the earlier the gestational age, the more difficult the dilemma. In patients who are close to 32 weeks of gestation, delivery would avoid continuous exposure to microbial products and inflammatory agents and is unlikely to increase neonatal morbidity. These patients are managed in our unit with detailed counseling, antibiotic administration, and delivery. In contrast, in patients close to 24 weeks of gestation, the option of parenteral administration of antibiotics is considered to eradicate intra-amniotic infection and

inflammation. Patients are informed that this alternative may prolong pregnancy, eradicate intra-amniotic infection, and reduce the risk of extreme prematurity, but that it requires intensive surveillance and repeat evaluation of the amniotic cavity to ensure eradication of microorganisms and reduced intra-amniotic inflammation (as determined by the amniotic fluid white blood cell count). Despite these interventions, the risk for infection and prematurity are not eliminated. Broad coverage is recommended before the results of cultures are available and this approach modified once the specific microorganisms involved are identified. The choice of antibiotics is informed by the results of microbial cultures. Our choice for broad coverage antibiotics includes azythromycin, clindamycin, and ampicillin. We have also used a combination of ceftriaxone, clindamycin and erythromycin for 10-14 days.[87] Azythromycin is included because *Ureaplasma urealyticum* is the most frequent microorganism found in the amniotic cavity.[67]

Antibiotic treatment aimed at the eradication of intra-amniotic infection should not be confused with the prophylactic treatment, which is now the standard of care for patients with preterm PROM, regardless of whether the inflammatory/infection state of the amniotic fluid is known. Thus, patients in this gestational age range, without evidence of infection and inflammation, are given prophylactic treatment with antibiotics (ampicillin and erythromycin). The patient in whom an amniocentesis cannot be performed is managed taking into account the results of biophysical testing, and antibiotics and steroids are administered.

In summary, the management of PROM between 24 and 31 completed gestational weeks is comprised of: 1) maternal and fetal inpatient surveillance in a tertiary medical center; 2) administration of corticosteroids to accelerate fetal lung maturity;[234] and 3) antibiotic administration, which may be therapeutic or prophylactic.[235;236]

1. "Prophylactic" antibiotic administration: Antibiotic administration has now become standard of care in patients with preterm PROM. This practice is based upon results of several randomized clinical trials, in which antibiotic administration is associated with prolongation of pregnancy, a reduced rate of maternal chorioamnionitis[237] and a reduced frequency of neonatal morbidity, measured as "composite neonatal outcome".[238] This approach has been often referred to as "prophylactic" antibiotic administration. However, this may be a misnomer. One-third of women with preterm PROM have a positive amniotic fluid culture on admission;[39] furthermore, the frequency of microbial invasion of the amniotic cavity increases as the patients are being observed in the antepartum ward to the point that at the time of the onset of labor, 75% of patients will have a positive amniotic fluid culture for microorganisms.[68] These studies were conducted before the administration of prophylactic antibiotics and demonstrate that microorganisms are present at admission and that secondary infection of the amniotic cavity occurs during expectant management. It would be inaccurate to refer to "prophylactic" administration as therapy instituted with patients who have a proven infection (1/3 of all patients). Anti-microbial therapy may prolong pregnancy by controlling microbial proliferation of an existing infection and preventing secondary infection/inflammation. However, antibiotic administration is not uniformly efficacious in eradicating microbially-proven intra-amniotic infection.[87]

Several investigators have conducted randomized clinical trials to assess the potential benefits of prophylactic antibiotic administration in patients with preterm PROM.[238-251] Mercer et al.[251] reported a randomized clinical trial in which patients were allocated to receive intravenous ampicillin (2 g every 6 hours) and erythromycin (250 mg every 6 hours for 48 hours, followed by oral amoxicillin and erythromycin base (every 8 hours for 5 days) versus placebos. Recruitment

was restricted to patients with a gestational age ranging between 24 to 32 weeks. GBS carriers were identified and treated, and tocolysis and steroids were not administered after randomization. The primary outcome of the trial was a composite variable that included any of the following: fetal or infant death, RDS, severe IVH, stage II or III of NEC, or sepsis within 72 hours of birth.[251] Antibiotic administration was associated with prolongation of pregnancy and a significant reduction in the rate of RDS [RR: 0.83, 95% CI: 0.69-0.99], NEC [RR: 0.4, 95% CI: 0.17-0.95], clinical chorioamnionitis, and the composite primary outcome, which is an index of fetal/infant morbidity and mortality [RR: 0.84, 95% CI: 0.71-0.99]. These differences were not demonstrated in GBS carriers, an observation attributable to antibiotic administration to patients allocated to the placebo group for this clinical indication, and thus obscuring the potential effects of antibiotic administration.[251]

In the ORACLE study,[238] 4,826 women with preterm PROM were randomly assigned to 1) erythromycin; 2) co-amoxiclav (amoxicillin and clavulanic acid); 3) erythromycin and co-amoxiclav; and 4) placebo. The study included patients before 36-6/7 weeks from 161 medical centers. Tocolysis and corticosteroid administration was left to the discretion of the attending physician. The primary outcome measure was a composite variable, which included neonatal death, chronic lung disease or major cerebral abnormality before discharge from the hospital. Among neonates of patients with singleton gestations allocated to erythromycin only, fewer had the primary composite outcome than those in the placebo group [11.2% vs. 14.4%, p=0.02]. Erythromycin treatment alone significantly reduced the proportion of patients delivering within 48 hours in comparison to the placebo group. The combination of erythromycin with co-amoxiclav significantly reduced the proportion of patients delivering within a week of admission. Similarly, co-amoxiclav administration alone, or in combination with erythromycin,

significantly reduced the proportion of patients delivering within 48 hours and within 7 days from admission, compared to the placebo group.[238]

The neonatal effects of erythromycin treatment included a reduction in the need for exogenous surfactant, in neonates needing 21% O_2 administration for 48 hours after delivery, as well as a reduction of the positive neonatal blood cultures.[238] Co-amoxiclav had a similar effect on the proportion of neonates needing 21% O_2 administration for 48 hours after delivery. Of note, the rate of suspected and proven NEC was significantly higher in the group of neonates whose mothers were treated with co-amoxiclav as a single or combined therapy. The authors attribute their findings to the wide and non-specific effect of this broad-spectrum antibiotic that may change the flora of the premature neonates and induce growth of pathologic bacteria that induce NEC.[238]

Lovett et al. did not demonstrate an association between prophylactic antibiotic treatment of patients with preterm PROM with co-amoxiclav and an increased incidence of NEC in comparison to placebo.[252] The studies differ in the antibiotic regimen, as well as in the gestational age at inclusion and the number of patients. Therefore, comparison of the studies is difficult. The recommendation of the investigators in the ORACLE I trial was to use erythromycin and avoid using co-amoxiclav in patients with preterm PROM.[238] Recently, a systematic review by Kenyon et al. confirmed these results.[253]

According to Kenyon et al., the number of patients needed to treat to prevent one adverse outcome remains high [chorioamnionitis - 10 (95% CI: 7-34); delivery within 48 hours - 9 (95% CI: 6-20); delivery within 7 days - 7 (95% CI: 5-15); neonatal infection - 17 (95% CI: 12-50); abnormal cerebral ultrasonography before discharge - 69 (95% CI: 35-1842)].[253] It is possible

that the wide confidence intervals reflect the range of gestational ages of patients included in the systematic review.

The follow-up of children to the age of seven enrolled in the ORACLE trial has demonstrated that any antibiotic treatment (erthromycin or co-amoxiclav) did not have a significant effect on the overall level of behavioral difficulties, on specific medical conditions on the proportion of children achieveing each level in reading, writing, or mathematics.[254] Therefore, it seems that the short-term benefits of antibiotic administration do not result in detectable differences in outcome at the age of seven.

2. Can antibiotic treatment of women with documented intraamniotic infection alter the natural history of preterm PROM? The traditional view has been that clinical chorioamnionitis should be managed by immediate delivery and this view has been extended to the management of subclinical intraamniotic infection.[255] There is evidence that both of these conditions can be treated *in utero* without interruption of pregnancy. Ogita and colleagues first reported the successful treatment of established chorioamnionitis with antibiotic treatment via a transcervical catheter.[256] Subsequently, we reported that giving antibiotics to a mother with preterm PROM at 29 weeks and an amniotic fluid culture positive for *Bacteroides bivius*, *Veillonella parvula*, and *Peptococcus* without clinical signs of chorioamnionitis resulted in eradication of MIAC.[257] In a second case, we were successful at eradicating *U. urealyticum* from the amniotic cavity with antibiotic treatment.[258]

The effects of antibiotics on the natural history of microbial invasion of the amniotic cavity in patients in preterm PROM has been reported by Gomez et al.[87] Patients who underwent amniocentesis upon admission and those without evidence of intra-amniotic inflammation or MIAC were treated with ampicillin and erythromycin for 7 days. In contrast, patients with intra-

amniotic inflammation or MIAC were treated with ceftriaxone, clindamycin and erythromycin for 10-14 days. Patients who remained undelivered after the conclusion of the course of antibiotics underwent a second amniocentesis. Six of seven patients who had MIAC at the time of the first amniocentesis still had positive amniotic fluid cultures for microorganisms after a full course of antibiotic treatment. Of the 18 patients with intra-amniotic inflammation, most (15/18) still showed evidence of an elevated white blood cell count in amniotic fluid after antibiotic administration. Therefore, antibiotic administration did not eradicate MIAC or intra-amniotic inflammation. Moreover, among patients with no evidence of intra-amniotic inflammation, 32% developed inflammation despite therapy and among those without MIAC, 55% developed a positive amniotic fluid culture.[87] These data raise important questions about the effect of antibiotics and the nature of the invading microorganisms in preterm PROM.

3. Should corticosteroids be administrated to patients with preterm PROM remote from term? A systematic review included 13 randomized clinical trials and demonstrated a reduction in the incidence of RDS, IVH and NEC [RR: 0.56, 95% CI: 0.46-0.70; RR: 0.47, 95% CI: 0.31-0.70; RR: 0.21, 95% CI: 0.05-0.82, respectively).[259] A non-significant trend of reduced neonatal mortality was observed; moreover, no increase in neonatal and fetal infection was observed.[259] Steroid treatment was associated with a modest, yet significant, increase in the risk of puerperal endometritis [RR: 2.42, 95% CI: 1.38-4.24], but no significant increase in neonatal sepsis. Similar findings were reported in an earlier meta-analysis, which included fewer trials, by Crowley.[260;261]

Clinical investigators have compared expectant management to steroid administration for 48 hours followed by delivery. However, induction of delivery immediately after steroid administration is associated with an increased risk of RDS and, therefore, is best avoided.[261] The

1994 National Institutes of Health Consensus Conference recommended the use of corticosteroids in pregnancies complicated by preterm PROM with expected delivery between 24 and 30 to 32 weeks of gestation.[234] This recommendation was based largely on data suggesting that the incidence of IVH was lower in neonates exposed to corticosteroids.[234] The modest increased risk of puerperal infection is considered easy to manage. A meta-analysis comparing the outcome of treatment with antibiotics and steroids versus antibiotics without steroids found that steroid administration diminished the beneficial effects of antibiotics in reducing the rate of chorioamnionitis, endometritis, neonatal sepsis, and IVH.[262]

4. How many courses of corticosteroids should be administered? Repeated courses of corticosteroids have been used to enhance their effects. However, recent data have raised questions about the safety of repeated corticosteroid administration based upon studies in humans and animals. Guinn et al. performed a double-blind randomized controlled trial, where women at risk for preterm delivery received one course of betamethasone or dexamethasone at admission, and were randomly allocated for subsequent weekly courses of either betamethasone or placebo until 34 weeks of gestation or delivery.[263] There were no significant differences in the frequency of composite neonatal morbidity (severe RDS, bronchopulmonary dysplasia, severe IVH, periventricular leukomalacia, proven sepsis, NEC, or perinatal death) between the study groups [weekly course: 22.5% vs. single course: 28%, p=0.16]. However, when the analysis was stratified by gestational age, patients that delivered between 24-27 weeks who received a single course had a higher rate of composite neonatal morbidity and severe RDS than those in the weekly course group. An important limitation of this study is that the authors did not control for the use of surfactant, which was more frequent in the single course group [single

course: 24% vs. weekly course: 15.6%, p=0.01].[263] This subject is covered in detail in the chapter on preterm labor.

5. Tocolysis:

Meta-analysis of the four randomized trials of tocolysis in preterm PROM[264-267] indicates that tocolysis does result in prolongation of pregnancy of more than 48 hours. However, no study has shown an improvement in maternal or neonatal outcomes. Therefore, there is no evidence to support the use of intravenous tocolysis in women with PROM.

6. Should a cervical cerclage be removed in a patient who presents with preterm PROM:

Cerclage removal has been advocated to reduce the risk of infection-related complications,[268] while leaving the cerclage in place has been recommended to prolong pregnancy. Yeast and Garite reported the results of a case-control study in which the outcome of patients with cervical cerclage removed after preterm PROM was compared with that of patients with PROM of a similar gestational age.[269] There was no difference in the incidence of chorioamnionitis or other infectious complications and neonatal outcome between the two groups. The interval between PROM and delivery was not significantly different between patients with and without cerclage. Blickstein and associates reported similar findings after comparing the outcome of 32 patients with cerclage and 76 without cerclage.[270] In contrast, Goldman and colleagues compared the outcome of 46 women with preterm PROM in whom the cerclage was not removed with that of 46 women with preterm PROM without cerclage.[271] Patients with a cerclage had a significantly shorter PROM-to-delivery interval and lower gestational age at delivery than patients without the cerclage. However, the rates of chorioamnionitis, other infection-related complications, and neonatal outcome were not different between the two groups. Ludmir et al. evaluated the role of immediate cerclage removal in

preterm PROM in 30 women.[272] In 20 women, the cerclage was removed immediately after the diagnosis of ruptured membranes was made; while in 10 women, the cerclage was retained after the membranes ruptured. Thirty-three patients with preterm PROM without cerclage served as controls. A greater proportion of women with a cerclage left in place delivered after 48 hours [90% vs. 50%, respectively]. However, perinatal mortality was significantly higher in infants born to women in whom cerclage was retained in comparison to immediate removal or the control group [70% vs. 10% vs. 18%, respectively]. Seventy-one percent of the neonatal morbidity was attributable to sepsis. The authors did not use broad-spectrum antibiotic treatment, which may explain this observation.[272]

McElrath et al. reported a randomized clinical trial conducted over 12 years comparing removal versus non-removal of cerclage in patients with preterm PROM.[273] All patients were treated with antibiotics and corticosteroids. Patients with retained cerclage had a lower gestational age at membrane rupture and delivered earlier than patients in which cerclage was removed. However, there was no difference in the latency period between the groups. Neonatal mortality was higher among patients in whom the cerclage was kept. This difference became non-significant, when the analysis was stratified into three gestational age groups (<28, 28-30, and >30 weeks). There were no significant differences in the rate of RDS, IVH and neonatal sepsis between the study groups.[273]

In summary, the evidence indicates that patients with preterm PROM and a cerclage could be managed by leaving the cerclage in place and maintaining close surveillance to detect maternal and/or fetal infection. However, removal of the cerclage is a legitimate alternative.

7. Home care vs. hospital care: Practice Bulletin #80 of the American College of Obstetricians and Gynecologists[274] stated that the safety of expectant management at home has not been

established; although, management of selected patients at home with careful observation has been reported. The potential disadvantages of home care include the risk of delivering a preterm infant outside a tertiary center and the implicit delay in obstetric intervention if fetal distress or infection occurs. The advantages of home care include decreased costs and psychological benefits to the patient.

Two studies have compared home care with hospital care. The first, a small, randomized trial of women with PROM at less than 37 weeks of gestation, had strict criteria for home care.[275] Only patients undelivered after 72 hours (60% delivered in less than 72 hours), in cephalic presentation, with negative amniotic fluid culture (by amniocentesis), cervical dilation of less than 4 cm on speculum examination, and at least one amniotic fluid pocket of more than 1 cm (22% had oligohydramnios) were eligible for participation. Follow-up included biweekly NST, weekly ultrasound examination, and corticosteroid administration. Fifty-five patients were randomized, 27 to home care and 28 to remain in-hospital. There was no difference in the latency period, gestational age at delivery, chorioamnionitis [11.1% vs. 14.3%], neonatal morbidity [3.7% vs. 7.1%], RDS [3.7% vs. 7.1%] or neonatal pneumonia [18.5% vs. 10.7%].[275]

The second study of home care was a retrospective study of patients with preterm PROM between 20 and 30 weeks of gestation, in which 19 of 21 women undelivered after 7 days were discharged home.[276] All patients had "adequate or slightly diminished amniotic fluid volume." Eleven of 19 women delivered at term. No neonatal deaths occurred, and there was one case of maternal and neonatal sepsis in a woman managed at home (she was infected with human immunodeficiency virus). One case of neonatal sepsis occurred in an infant born to a woman who was managed in-hospital and delivered preterm.

The data available are insufficient to recommend management of preterm PROM outside tertiary-care centers. We believe that fetuses with preterm PROM require careful surveillance, which is rarely available outside a hospital environment.

8. When is the appropriate time for induction? Expectant management of patients presenting with preterm PROM remote from term is today the standard of care.[20;235;236] This management significantly reduces the neonatal complications related with prematurity;[20;235;236] however, the longer the latency period, the higher the risk for chorioamnionitis and abruption.[202;277-279]

Cox and Leveno performed a prospective study comparing induction versus expectant management of patients presenting with preterm PROM between 30-34 weeks. There were no significant differences in neonatal morbidity. However, the frequency of chorioamnionitis was significantly higher in the expectant management group [2% vs. 15%, p=0.009]. Of note, 74% of the expectant management group delivered within 72 hours.[280]

The timing of delivery is a determinant of the presence of major, but not minor, composite neonatal morbidity. Indeed, major composite neonatal complications (RDS, IVH, intubation, BPD, seizure, NEC, bowel perforation, retinopathy of prematurity (ROP), meningitis, pneumonia primary pulmonary hypertension, and patent ductus arteriosus) decrease substantially after 32 weeks of gestation.[281] In contrast, minor composite neonatal outcomes (hyperbilirubinemia, transient tachypnea of the newborn, hyper- or hypoglycemia and hyper- or hyponatremia) decrease only after 34 weeks of gestation. Mercer et al. demonstrated that in patients with preterm PROM, delivery after 32 weeks of gestation was not associated with a significant increase in neonatal morbidity.[203] The development of chorioamnionitis, placental abruption or a non-reassuring fetal heart rate tracing often requires induction of labor and delivery, regardless of gestational age.

PROM Near Term (32-36 Weeks of Gestation) (see Figure 5): Mercer et al. demonstrated that there were no differences in the maternal and neonatal outcomes of expectant management and induction of labor at this gestational age window.[203] However, there was a trend toward a higher incidence of chorioamnionitis in the expectant management group.[203] Cox and Leveno reported a higher incidence of chorioamnionitis.[280] One approach to management is to perform an amniocentesis for fetal lung maturity between 32-34 weeks and if the result is mature, to proceed with induction of labor in order to reduce maternal morbidity.[235;280;282] In cases with negative fetal lung maturity, the management is not clear. Some physicians will choose expectant management until 34 weeks, while others will administer corticosteroids and induce labor 48 hours later.[283] There are not sufficient data in the literature to support either course of action. In a survey that was conducted in the USA during 2003 among members of the Society of Maternal Fetal Medicine, 42% will induce labor in patients presenting with premature PROM and positive lung maturity at 32 weeks.[283] In cases with unknown fetal lung maturity, 58% will postpone delivery to 34 weeks of gestation.[283]

In summary, patients between 32 and 34 weeks need assessment of lung maturity; and, if the profile is consistent with maturity, the patients could be offered induction of labor. In cases without evidence of fetal lung maturity, there are not sufficient data as to the optimal management approach. Mercer et al. proposed that women with PROM after 34 weeks should be delivered.[12]

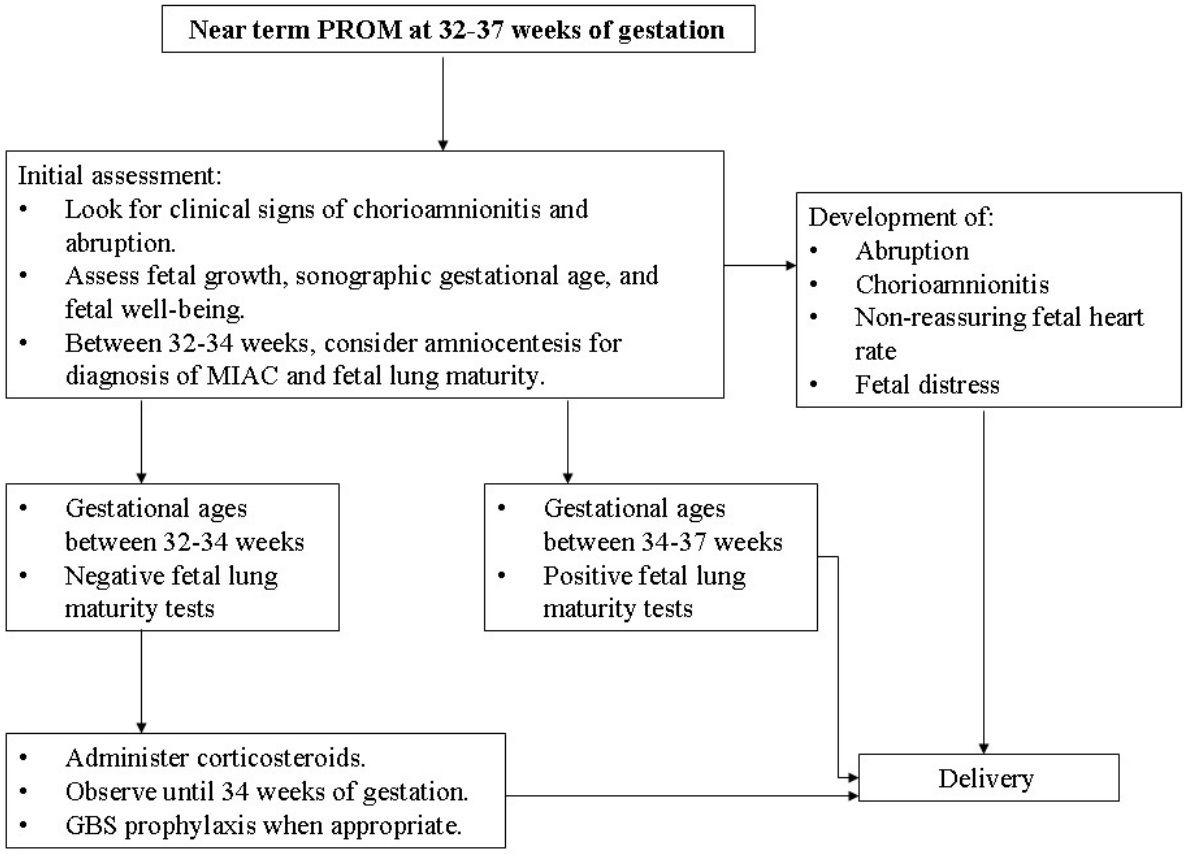

Figure 5

PRELABOR RUPTURE OF THE MEMBRANES AT TERM

The management of patients with PROM at term includes: 1) exclusion of cord prolapse; 2) detection of infection, and 3) evaluation of fetal well-being. If any evidence exists of fetal compromise or infection, induction of labor or delivery is the management of choice. For other patients, the relevant management issues include deciding between (a) induction or expectant management and (b) when and how induction should be undertaken.[284-307]

The natural history of term PROM is that 90% of women will be in spontaneous labor within 24 hours.[307] Nulliparous women have a longer latency period than do multiparous

women.[290;297;302] Patients with an unfavorable cervix at presentation and those who are not in labor within 6 hours of rupture of membranes generally do not initiate labor spontaneously within 24 hours and represent a management dilemma.[306]

The largest clinical trial in term PROM[291] included 5,041 patients who were randomly allocated to four groups: 1) immediate induction with oxytocin; 2) expectant management followed by induction with oxytocin after 4 days; 3) induction of labor with vaginal prostaglandin E_2 (1-2 mg, followed by IV oxytocin; if not in labor in 4 hours, a second dose of prostaglandin E2); and 4) expectant management followed by induction of labor with prostaglandin E_2, if labor had not begun within 4 days. The primary outcome of the trial was probable neonatal infection (clinical and laboratory signs). Secondary outcomes were the need for cesarean delivery and women's evaluation of their treatment. The results showed no difference in neonatal infection and cesarean delivery rate between the induction groups (oxytocin vs. prostaglandin E_2). However, the incidence of chorioamnionitis was lower in patients allocated to induction of labor. Women's satisfaction with their obstetric care was higher for those allocated to induction of labor.

Mozurkewich and Wolf in their meta-analysis of 23 studies including 7,493 women, demonstrated that induction of labor is superior to expectant management.[298] The meta-analysis compared three policies: 1) immediate induction with oxytocin; 2) induction of labor with vaginal or endocervical prostaglandin E_2 gel suppositories or tablets; and 3) expectant management that sometimes has included delayed induction with oxytocin. The frequency of chorioamnionitis and endometritis was significantly lower in patients undergoing immediate induction of labor with oxytocin than in those managed expectantly [OR: 0.67, 95% CI: 0.52-0.85 and OR: 0.71, 95% CI: 0.51-0.99, respectively]. The rate of chorioamnionitis was

significantly higher in patients who received vaginal prostaglandins than in those induced with immediate administration of oxytocin but lower than that of patients in the expectant management group [OR: 1.55, 95% CI: 1.09-2.21 and OR: 0.68, 95% CI: 0.51-0.91, respectively]. The rates of cesarean delivery and neonatal infection were not different among the three management schemes. Based on this data, we endorse a policy of immediate induction of labor in patients with term PROM. Antibiotic administration is justified before cesarean delivery for obstetric indications or for carriers of GBS.

Tan and Hannah[308] performed a meta-analysis of 18 trials comparing induction of labor with oxytocin versus expectant management in patients with PROM at or near term. Induction of labor with oxytocin was associated with a lower risk of chorioamnionitis [OR: 0.63, 95% CI: 0.51-0.78], endometritis [OR: 0.72, 95% CI: 0.52-0.99], and neonatal infection [OR: 0.64, 95% CI: 0.44-0.93]. Cesarean delivery rates were not statistically different. Oxytocin was associated with a more frequent use of pain medication and internal fetal heart rate monitoring. Another meta-analysis of 15 RCTs by Lin et al. included: 1) six studies [n=453] of misoprostol versus placebo or expectant management; and 2) nine studies [n=1,130] of misoprostol versus oxytocin for labor induction with term PROM.[309] There were no significant differences in the frequency of chorioamnionitis, neonatal sepsis, or caesarean delivery among study groups.

Expectant management at home of patients with PROM at term is not recommended. This recommendation is based upon the report of Hanna et al. that home care was associated with an increased risk of neonatal infections [OR: 1.97, 95% CI: 1.00-3.90] and cesarean delivery in patients not colonized with GBS [OR: 1.48, 95% CI: 1.03-2.14].[310]

FIGURE LEGENDS

Figure 1. Rupture of membranes as a function of cervical dilatation and state of labor. Percentage distribution for 517 normal spontaneous deliveries without medication or maneuvers; vertex presentation.[21]

Figure 2. Initial assessment of preterm PROM. [AFI = amniotic fluid index; GBS = Group B *Streptococcus*]. Modified from Mercer, B.M. [235]

Figure 3. Management of previable PROM (before 24 weeks of gestation). [MIAC = microbial invasion of the amniotic cavity]. Modified from Mercer, B.M.[235]

Figure 4. Management of PROM remote from term (between 24-31 6/7 weeks of gestation). [MIAC = microbial invasion of the amniotic cavity; NICHD = National Institute of Child Health and Human Development, NIH/DHHS]. Modified from Mercer, B.M.[235]

Figure 5. Management of near term PROM (between 32-37 weeks of gestation). [MIAC = microbial invasion of the amniotic cavity; GBS = Group B *Streptococcus*]. Modified from Mercer, B.M. [235]

TABLES

Table 1. Risk factors associated with preterm PROM (at less than 35 weeks) stratified by parity.[25]

	Nulliparous		Multiparous	
Risk Factor	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Cervical length ≤ 25 mm	9.9	3.8-25.9	4.2	2.0-8.9
Previous preterm birth with preterm PROM	--	--	4.1	2.0-8.7
Previous preterm labor with intact membranes	--	--	2.6	1.2-5.3
Working during pregnancy	5.3	1.5-18.7	n.s.	n.s.
Medical complications	4.2	1.1-16.0	n.s.	n.s.
FFN (+)	n.s.	n.s.	n.s.	n.s.
BV	n.s.	n.s.	n.s.	n.s.
FFN (+) and absent BV	n.s.	n.s.	9.0	3.6-22.5
FFN (-) and present BV	n.s.	n.s.	2.8	1.2-6.3

FFN = fetal fibronectin; BV = bacterial vaginosis; n.s. = non-significant. Modified from Mercer et al.[25]

TABLE 2.[85;187] Diagnostic indices and predictive values of different amniotic fluid tests in the detection of positive amniotic fluid culture in patients with premature rupture of the fetal membranes.

Amniotic Fluid Tests	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
Gram's stain[187]	34.8	96.4	88.9	63.9
IL-6 (≥7.9 ng/mL)[85]	80.9	75	66.7	86.4
MMP-8 (>30 ng/mL)[187]	76.1	61.8	62.5	75.6
WBC count (≥30 cells/μL)[187]	55.6	76.4	65.8	67.7
WBC count (≥50 cells/μL)[85]	52.4	83.8	66.7	74
Glucose (<10 mg/dL)[85]	57.1	73.5	57.1	73.5
Glucose (<14 mg/dL)[85]	71.4	51.5	47.6	74.5
Gram's stain + WBC count (≥30 cells/μL)[187]	62.2	76.4	68.3	82.5
Gram's stain + glucose (<10 mg/dL)[85]	66.7	73.5	60.9	78.1
Gram's stain + IL-6 (≥7.9 ng/mL)[85]	80.9	75	66.7	86.4
Gram's stain+ MMP-8 (>30 ng/mL)[187]	82.6	61.8	64.4	81
WBC count (≥30 cells/μL)+ MMP-8 (>30 ng/mL)[187]	80	60	62.1	78.6
Gram's stain + WBC count (≥30 cells/μL) + glucose (<10 mg/dL)[85]	76.2	60.3	54.2	80.4
Gram's stain + WBC count (≥30 cells/μL) + IL-6 (≥7.9 ng/mL)[85]	85.7	61.8	58.1	87.5
Gram's stain + WBC count (≥30 cells/μL) + MMP-8 (>30 ng/mL)[187]	84.4	60	63.3	82.5
Gram's stain + glucose (<10 mg/dL) + IL-6 (≥7.9 ng/mL)[85]	85.7	52.9	52.9	85.7
Gram's stain + WBC count (≥30 cells/μL) + glucose (<10 mg/dL) + IL-6 (≥7.9 ng/mL)[85]	92.9	47.1	52	91.4

IL, interleukin; WBC, white blood cell; MMP- matrix metallo protease

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