Preterm Premature Rupture of Membranes

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Abstract

Preterm premature rupture of membranes (PPROM) represents approximately 33% of preterm births and is a major factor contributing to perinatal morbidity and mortality. Many studies have been done in order to establish the best treatment option for the patients with PPROM. Yet, there are some controversies regarding this issue. Improving neonatal outcome by minimizing the infectious and prematurity risks is the main target. Management alternatives of pregnancies complicated with PPROM include immediate delivery and conservative treatment. The use of antenatal corticosteroids and antibiotics improve neonatal outcome, while tocolitycs have limited value in expectant management of PPROM.
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Epidemiology

Over the last three decades the incidence of preterm birth in developed countries has been estimated to represent about 5-7% of live births, while in the United States is approximately 12%. Although recent data show a slight increase in the incidence of preterm birth during the last years (e.g. in the USA it increased from 10.7% in 1992 to 12.3% in 2003), the rate of births before 32 weeks has remained constant, at 1-2%[1,2]. Increasing age of the mothers, more pregnancies obtained after infertility treatment, higher rates of multiple pregnancies, more obstetrical interventions are some factors that have contributed to the rise in the incidence of preterm birth. Preterm premature rupture of membranes (PPROM) is the most frequent cause of preterm birth (approximately 33%). It complicates 2% to 4% of singleton and 7 to 20% of twin pregnancies, being associated with 18-20% of all perinatal deaths[3].

Risk factors. Pathophysiology

Multiple factors are correlated to an increased risk of PPROM: black race, lower socioeconomic status, smoking, history of antepartum vaginal bleeding, cervical incompetence, previous operations involving the uterine cervix, uterine anomalies, uterine hyperdistension (polyhydramnios, multiple pregnancies). Previous PPROM is a major risk factor, the recurrence risk of PPROM being 16 % to 32 %[3,4,5]. Placental abruption is seen in 4 to 12% of pregnancies complicated by preterm PROM, and is more frequent in pregnancies before 28 weeks of gestation[2,3]. Collagen anomalies (decreased collagen content of the membranes or excessive collagen degradation), membrane localized defects, are also predisposing factors that increase the risk of PPROM. Amniocentesis, chorionic villus sampling, fetoscopy and cervical cerclage are rare causes of PPROM[4]. Numerous studies have demonstrated the correlation between lower and upper genital tract infection and PPROM. Compared to women with uncomplicated pregnancies, those with PPROM have a higher incidence of lower genital tract infections (group B streptococcus, Neisseria Gonorrhea, Trichomonas vaginalis, Gardnerella vaginalis). Also, patients with PPROM are more likely to have clinical/subclinical chorioamnionitis than women with preterm labor with intact membranes[6,7].

Choriodecidual inflammation/infection is by far, the most common etiological factor involved in the pathogenesis of PPROM. The rate of positive cultures obtained by amniocentesis at admission is approximately 25-40%. However, in the majority of cases, the clinical chorioamnionitis is not present. Only 1-2% of patients have clinical signs of chorioamnionitis and 3-8% will develop the symptoms late[4].

Diagnosis

Preterm PROM is mainly a clinical diagnosis. Patient history of watery vaginal discharge has an accuracy of 90% and should not be ignored[4]. The clinical examination using a sterile speculum may reveal fluid pooling in the vaginal vault or fluid leaking from the cervical os. Laboratory studies, such as nitrazine test or ferning test may help to confirm the diagnosis of ruptured membranes. The alkaline pH of amniotic fluid turns yellow nitrazine paper to blue. The presence of arborization (ferning) can be observed under o low-magnitude microscope, when the fluid has dried on the glass slide, indicating the rupture of membranes[8]. Although they are widely used, both tests have some pitfalls. The nitrazine test can give false positive results in the presence of blood, semen, bacterial vaginosis, Trichomonas infections, alkaline urine or alkaline antiseptics and the ferning test may be falsely positive in the presence of highly estrogenized cervical mucus, vaginal blood or exogenous saline on slide from a fingerprint[9].

Leopold's examination may suggest decreased amniotic fluid volume but it cannot confirm the diagnosis. Demonstration of severe oligohydramnios by ultrasonography in a patient with suggestive history also is helpful in setting the diagnosis of PPROM. When clinical examination, laboratory tests and ultrasonography are inconclusive, the instillation of a dye (Evan's blue, fluorescein, or indigo carmine) by amniocentesis may determine whether the membranes are ruptured[5,9]. When instillation of indigo carmine dye is performed, the blue dye passes onto a vaginal tampon within 20-30 minutes if the membranes are ruptured[10]. Given that the amnio-dye test is an invasive procedure with inherent risks (iatrogenic PROM, placental abruption, infection and miscarriage), a noninvasive method of testing is preferred.

Regarding the limitations of current tests for the diagnosis of PROM, several markers have been proposed by some investigators to diagnose membranes rupture, as alternative and more objective tests. Such tests are based on detecting in the cervical and vaginal secretions of one or more biochemical markers that are present in patients with ruptured membranes: alpha fetoprotein, fetal fibronectin, insulin-like growth factor binding protein 1, beta human chorionic gonadotropin, creatinine, placental alpha-microglobuin 1[3].

Complications

PPROM involves a wide range of both fetal and maternal complications. Neonatal complications are related to prematurity and infectious risks. Literature data show that PPROM is associated with a 4-fold increase in perinatal mortality and a 3-fold increase in neonatal morbidity[3]. Respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), fetal pulmonary hypoplasia, broncho-pulmonary dysplasia, necrotizing enterocolitis (NEC) and sepsis are major neonatal complications, their occurrence and severity being closely related to the grade of prematurity[3,6]. There is an increased rate of cesarean delivery in patients with PPROM due to high incidence of malpresentations, umbilical cord prolapse or compression. Fetal deformities (limb position defects, facial anomalies) may also occur in patients with PPROM and are related to duration and severity of membrane rupture[3]. Exposure of the fetus to intrauterine inflammation/infection has been associated with an increased risk of impaired neurological development[2]. Yoon, Romero et al have described the "Fetal Inflammatory response Syndrome". This phenomenon implies fetal infection prior to overt choriamnionitis and is responsible for the subsequent fetal central nervous system lesions, which may culminate in cerebral palsy[6].

Maternal complications include clinically overt choriamnionitis (13-60%) and puerperal endometritis (2-13%). These complications are more frequent in women with PPROM at early gestational age, with multiple local examinations, longer latency time and severe oligohydramnios[6,10].

Management

The management of PPROM is depending on gestational age. The main factors that must be considered in developing a management plan for PPROM are confirmation of diagnosis, assessment of an accurate gestational age, exclusion at admission of intra-amniotic infection, fetal malformation and fetal distress, and deciding on the mode of delivery. The availability of neonatal intensive care unit is also another important factor[3,9,10].

The options for the patient with PPROM are immediate delivery or conservative management. Each alternative involves potential complications for both mother and baby.

The expectant management has poor maternal benefits, but it can improve the neonatal outcome by decreasing the perinatal morbidity related to prematurity. The hazards associated with conservative management are the risks of ascending infection, umbilical cord prolapse or compression, placental abruption, emergent delivery for a non-reassuring fetal status or fetal death. Absolute contraindications of expectant management are: chorioamnionitis, non-reassuring fetal testing, placental abruption and active labor[4]. In patients with PPROM delivery is recommended when the risk of ascending infection outweighs the risk of prematurity[3]. Immediate delivery is associated with prematurity complications (RDS, NEC, IVH, sepsis).

Tocolytic therapy

Tocolytics have a limited value in the expectant management of PPROM. Prophylactic tocolysis may delay delivery for a short period (24 to 28 hours), while the therapeutic tocolysis has not been proven to prolog the latency period[2,3]. In a randomized double-blind study of women with PPROM, between 28-36 weeks, Christensen at al. compared ritodrine tocolysis to placebo. The latency period was prolonged for 24 hours, but with no evident clinical benefit. Other investigators (How et al) found no significant improvement in perinatal outcome, in a prospective randomized controlled trial, when comparing magnesium sulphate tocolysis to no tocolysis in patients with PPROM (24-34 weeks)[4].

Although, there is no strong evidence that tocolytic therapy can improve long-term perinatal morbidity or mortality, in the absence of contraindications (overt/subclinical chorioamnionitis, placental abruption, non-reassuring fetal testing or other maternal/fetal contraindications),

some authors recommend tocolytics for a short term to allow corticosteroids administration and maternal transport to a level II/III care unit[5,8]. The literature data do not support the use of tocolytic agents beyond the initial 48-hour steroid window[3,4,5].

Antenatal corticosteroid treatment

The administration of antepartum corticosteroids has clearly demonstrated the reduction of perinatal morbidity and mortality after PPROM. The corticosteroids do not only increase the lung maturation and production of surfactant. The incidence of RDS, NEC, IVH decreases by approximately 50% when using corticosteroid treatment in patients with pregnancies complicated with PPROM prior to 32 weeks of gestation[2,11,12]. The same benefits were not confirmed in pregnancies between 32-34 weeks of gestation, the use of corticosteroids in these patients being controversial. Administration of corticosteroids after 34 weeks of gestation is not recommended unless fetal maturity testing is negative[2,5,8].

The most widely used regimens include a single course of either betamethasone (two doses of 12 mg intramuscularly, 24 hours apart) or dexamethasone (four doses of 6 mg intramuscularly, 12 hours apart). The maximum beneficial effect is achieved 24 to 48 hours after the first dose, and it lasts for at least 7 days[3]. Multiple courses are not recommended because of a lack of additional benefits, and because of the potential adverse effects on fetal growth and neurodevelopment.

Antibiotherapy

The advantages of intrapartum Group B beta-hemolytic Streptococcus (GBS) chemoprophylaxis are well established. In women who known carriers of group B streptococci, there is now evidence that the antibiotic treatment during labor reduces the incidence of early-onset neonatal group B streptococcal sepsis and mortality[7]. The intrapartum antibiotic prophylaxis should be offered to all patients with unknown group B streptococcal status or with a history of positive culture during the present pregnancy[4]. Treatment is not initiated if a negative anovaginal culture has been documented within previous 5 weeks[3].

A minimum of 4 hours of antibiotics is recommended prior to delivery. The first line treatment is intravenous penicillin, but ampicillin is also a therapeutic option. In the presence of penicillin allergy, erythromycin or clindamycin can be used. In the United States cefazolin is recommended in women with an uncertain penicillin allergy or with minor allergic reactions[4].

Prophylactic Broad-Spectrum Antibiotics to Prolong Latency

The advantages and disadvantages of using broad spectrum antibiotics in the conservative management of PPROM have been widely studied. In most trials, use of antibiotics has been associated with prolongation of pregnancy and also with reduction in infant and maternal morbidity[2,8]. Antibiotics are valuable not only for their antimicrobial action; they also modulate the maternal and fetal inflammatory response that conducts to labor and neonatal morbidity[4].

One of the largest studies that have investigated the benefits of antibiotic use in PPROM was reported by Mercer et al. (NICHD study). Participants - women with PPROM between 24-32 weeks - were randomly assigned to treatment with placebo or intravenous ampicillin plus erythromycin for 48 hours, followed by oral amoxicillin plus enteric-coated erythromycin base for another 5 days. The trial found that antibiotics improved neonatal outcome by reducing the risk of death, early sepsis, respiratory distress syndrome, severe intraventricular hemorrhage and necrotizing enterocolitis (from 53% to 44%, P<0.05). The incidence of chorioamnionitis was also decreased and the latency prolonged for more than 7 days (in some cases the up to 3 weeks)[2,4,8].

Management based on gestational age

34 to 36 weeks

Considering the patients with pregnancies complicated with PPROM between 34-36 weeks of gestation, literature data do not support the conservative management. Studies have shown that expectant management between 34-36 weeks increases the risk of chorioamnionitis and there is no improvement in neonatal morbidity[13,14]. Appropriate group B beta-hemolytic streptococcus chemoprophylaxis should be administered, corticosteroids are not indicated because of the lack proven efficacy in improving perinatal outcome, and maternal transport to a level II/III care unit is strongly recommended.

32 to 33 weeks

Lung maturity assessment may be helpful to plan the timing of delivery in the 32-33 weeks of gestation range[4]. Amniocentesis performed at 32 weeks is not only helpful in assessment of pulmonary maturity but also in diagnosis of infection. If lung maturity tests are positive, delivery should be considered. When tests are negative or not available, the patients can be offered conservative management, with antibiotics and antenatal corticosteroids. Delivery is considered either after the corticosteroid benefit has been obtained (48 hours after the first dose), or at 34 weeks[5]. Close maternal and fetal surveillance is mandatory during the expectant management, in order to detect clinical/subclinical chorioamnionitis, non-reassuring fetal status or placental abruption.

24 to 31 weeks

Most of the patients with PPROM before 32 weeks of gestation have a latency period of one week. In the absence of intra-amniotic infection conservative management should be offered in order to prolong the pregnancy until 34 weeks of gestation. Transportation to a tertiary care unit, corticosteroids and antibiotic administration are indicated. Fetal well-being should be assessed by fetal monitoring or ultrasonography. The two more common testing modalities are non-stress test and biophysical profile, contraction stress test being contraindicated. There is no consensus about the frequency of this monitoring. Reasonable options are weekly, twice weekly, some authors recommending daily non-stress testing or biophysical profile[2]. In addition, maternal surveillance is also an important issue. The presence of maternal tachycardia, oral temperature exceeding 38°C, uterine tenderness or leukocytosis is indicative of amnionitis. Although the diagnosis of chorioamnionitis is clinical, amniocentesis may help to suggest (elevated amniotic fluid white cells count, elevated LDH level, decreased glucose concentration) or to confirm the diagnosis (positive Gram stain)[3,5]. Patients reaching 32-33 weeks of

gestation with a documented lung maturity should be considered for delivery. Also, at 34 weeks' gestation, or in the presence of chorioamnionitis or other complications (placental abruption, non-reassuring fetal status), delivery is indicated.

Conclusions

Preterm premature rupture of membrane is the most frequent cause of preterm birth and is associated with important maternal and fetal complications. PPROM contributes to 18-20% of all perinatal deaths. The neonatal outcome depends primarily on gestational age at presentation and delivery. A prompt and accurate diagnosis has a major role in improving neonatal prognosis. If not available, maternal transport to a level II/III care unit is strongly recommended. Immediate delivery and conservative management are the basic options in patients with PPROM. During expectant management maternal and fetal surveillance is required. Corticosteroids are of clear benefit before 32 weeks of gestation. Delivery should be considered in some patients after 32 weeks. After 34 weeks the benefits of elective delivery seem to exceed the risks. ■

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