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The management and clinical outcome in premature rupture of fetal membranes

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Abstract

Premature rupture of membrane (PROM) before 37 weeks gestation complicate 3-4.5% of pregnancies and represents almost 30% of causes of premature delivery. Dividing this pathologic entity according to gestational age has two reasons: the first is that we have a different management and the second is that the maternal and fetal complications but also the fetal prognosis is different with gestational age. In this review the therapeutic management in PROM, induction of labor versus conservative therapy for prolonged latent period are discuss.

Keywords: *premature rupture of membrane, tocolysis, corticosteroid*

Introduction

Premature rupture of membranes before 37 weeks of pregnancy complicates 3 to 4.5% of pregnancies, accounting for 30% of the causes of premature delivery[(1)]. Occurrence of premature rupture of membranes (PROM) before 26 weeks of pregnancy was considered a decade ago a pathology that occurs below the fetal viability. With the advancement of postnatal care resources, fetal viability limit continues to decline so we can divide premature rupture of membranes according to gestational age as follows: rupture of membranes before fetal viability limit, under 23 weeks gestation; premature rupture of membranes between 24 and 31 weeks and rupture of membranes near delivery term, between 32-36 weeks. Dividing this condition depending on gestational age is necessary for two reasons, one being the different therapeutic conduct applicable to these cases, and another reason is imposed by maternal and fetal complications that arise in cases of premature rupture of membranes, as well as different fetal prognosis depending on the gestational age at which it appears[(1)].

The etiology of premature rupture of membranes

Fetal membranes are represented by two different histologically structures, a thin layer - the amnion, delimiting the amniotic cavity, and the chorion which comes in direct contact with maternal decidua, structures that merge at the end of the first trimester of pregnancy.

As gestational age advance, changes occur in the connective structure of the fetal membranes and cellular apoptosis, which will cause weakening of these structures. Premature rupture of membranes may occur in cases of accelerated physiological process of fetal membrane weakening resistance. Pathophysiological, a local growth of the cytokines occurs, an unbalanced interaction between local metalloproteinases (MMP-1, MMP-2, MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1, TIMP-3) as well as the activation of collagenases and other proteases that will destroy the connective matrix of the membranes[(2)]. This mechanism is the final result of several etiological factors, such as: urogenital infections, congenital connective tissue disorders (Ehlers-Danlos syndrome), uterine over distension, symptomatic uterine contractions, bleedings in the second and third trimesters, copper and ascorbic acid deficiencies, smoking, prior cervical surgery.

The urogenital tract infections are the most common etiologic factor involved in the occurrence of premature rupture of membranes. Pathogens commonly associated with PROM are *Neisseria gonorrhoeae*, *Mycoplasma sp.*, *Ureaplasma sp.*, *Mobiluncus sp.*, *Bacteroides sp.*, *Gardnerella vaginalis*, *Trichomonas vaginalis* and group *B Streptococcus*[(3,4)]. In terms of group *B Streptococcus*, not only vaginal colonization with this germ is associated with PROM, but also group B Streptococcal bacteriuria is frequently involved in the development of this pahtology[(5)]. Although premature rupture of membranes is an acute phenomenon, due to the frequent association with urogenital infections, it may be considered that it is based on subacute or chronic inflammatory phenomenon, secondary to early onset genital infections in the beginning of the second trimester[(6)].

The management in cases of premature rupture of membranes

The management in PROM is based on individualization of the case based on fetal and neonatal complications risk assessment, thus directing us to a conservative management or induction of labor. Maternal morbidity must also be taken into account, especially in cases of premature rupture of membranes occurred below the fetal viability (under 23 weeks) (Figure 1).

Therapeutic conduct in premature rupture of membranes between 32-36 weeks

Premature rupture of membranes between 34-36 weeks of pregnancy requires as management the induction

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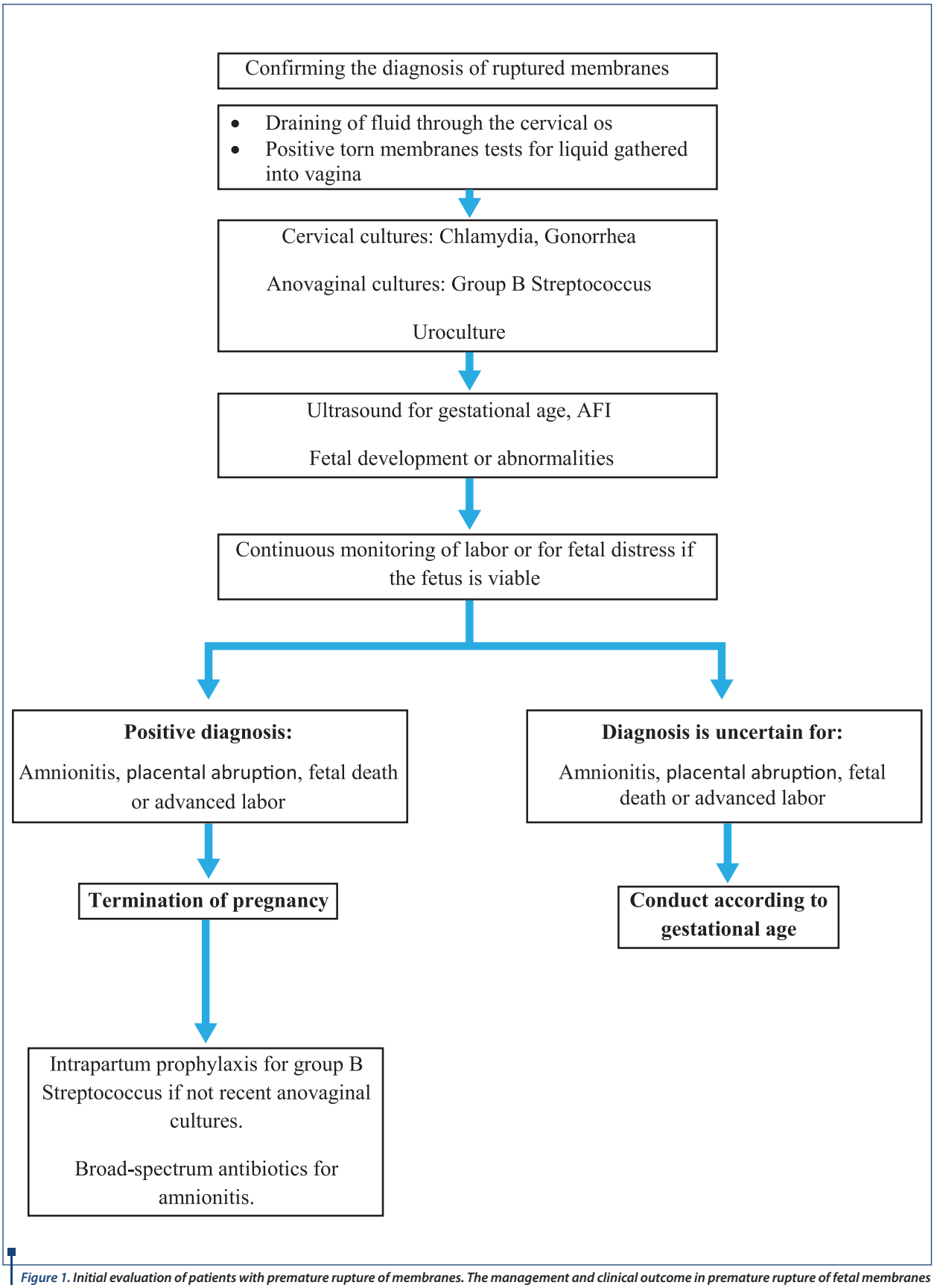

Figure 1. Initial evaluation of patients with premature rupture of membranes. The management and clinical outcome in premature rupture of fetal membranes

of labor without prior administration of corticosteroids for accelerating fetal lung maturation. This behavior is guided mainly by the low rate of severe neonatal complications occurring after 34 weeks compared with the increased risk of chorioamnionitis for a conservative behavior of postponing the birth.

The study on 120 PROM cases occurring between 34-36 weeks evaluates an increased risk of chorioamnionitis (16% versus 2%, p = 0.007) and low pH in fetal blood collected from the umbilical cord (7.35 versus 7.25, p = 0.009) in cases treated conservatively without neonatal improved prognosis(7).

Similar results are reported by other retrospective studies regarding conservative treatment versus onset of birth in cases with PROM after 34 weeks(8, 9).

Antibiotic treatment is necessary especially in patients carrying group B streptococcus or those whose test was not performed for detecting infection with this germ. Therapeutic attitude for PROM between 32-33 weeks of gestation is controversial. Conservative treatment's benefits of improving fetal lung maturity should be weighted with the risk of fetal infection. Antibiotic prophylaxis that is administered in cases of premature ruptured membranes is explained by the fact that this condition is often triggered by a latent infection of the lower pole of the amniotic sac. Early antibiotic treatment cannot prevent the appearance of chorioamnionitis because of low bioavailability of the antibiotics in the amniotic fluid and in the fetal tissues and intraamniotic infection may be latent, sometimes with onset before the rupture of membranes. PCR and proteomics analysis allowed intraamniotic identification of a significant number of germs in 24-48 hours after rupture of membranes[9].

Given the increased risk of colonization of the amniotic cavity with bacteria after PROM the best approach is assessing fetal lung maturity by amniotic fluid analysis to further guide the therapeutical approach. Amniotic fluid analysis can be performed on fluid samples obtained by collecting it from the vagina or amniocentesis. Amniocentesis in the presence of oligoamnios is often difficult to execute. To assess the degree of lung maturity in amniotic fluid we can calculate the lecithin/sphingomyelin ratio, qualitative or quantitative determination of phosphatidylglycerol, the surfactant/albumin ratio or quantify the lamellar corpus produced by type II pneumocyte. All these parameters have a predictive value between 96-100% in the evaluation of lung maturity but predictive value regarding pulmonary immaturity is below 50%. Analysis of amniotic fluid collected from the vagina (at least 3 ml) involves evaluation of the surfactant/albumin ratio and identification of the phosphatidylglycerol produced by fetal type II pneumocyte. Identification of phosphatidylglycerol, although it has the advantage of not being influenced by sample contamination with blood or vaginal mucus, is frequently negative below 36 weeks of gestation[10].

If pulmonary maturity is proved, the birth can be induced in cases of PROM occurred between 32-33 weeks without prior corticotherapy. In cases of fetal lung immaturity corticosteroids are administered to accelerate lung maturity, antibiotics for prophylaxis of neonatal infections and the latent period to the onset of labor is prolonged. It is desirable to choose a single antibiotic, the most active, the least toxic to the fetus (if possible bactericidal) and the least supposed to lead to bacterial resistance. It is preferred to administer beta-lactam class antibiotics (penicillins or cephalosporins) or combination of beta-lactams with beta-lactamase inhibitors. Macrolides that have bacteriostatic effect and aminoglycosides with significant adverse effects on the fetus are not part of first-line antibiotics. Antibiotic therapy is guided by the antibiogram obtained by testing the susceptibility from the isolates of cervical germs, amniotic fluid or vaginal discharge.

Therapeutic conduct in premature rupture of membranes between 26-31 weeks

The birth of a fetus before 32 weeks is burdened by severe neonatal morbidity and an increased risk of postnatal mortality. In the absence of the chorioamnionitis signs, the clinician must ensure extension of pregnancy as close to 34 weeks as possible. He must also prevent the patient and the family that despite medical efforts, in most cases the birth occurs in a week after the rupture of the membranes[11].

Contraindications of the conservative treatment to extend the pregnancy are represented by chorioamnionitis, abruptio placentae or signs of acute fetal distress.

In case of conservative treatment, corticosteroids and antibiotics are administered and cardiotocography and ultrasound fetal monitoring is ensured in order to detect early signs of fetal distress. Because the umbilical cord compression due to oligohydramnios is common in cases of PROM arising before 32 weeks of pregnancy cardiotocography is recommended daily or continuous during labor.

The presence of the oligoamnios does not influence the maternal or fetal infectious morbidity, but is significantly correlated with decreased latency time between rupture of membranes and onset of labor[12].

The length of the latency period before the onset of labor does not correlate with neonatal morbidity. In cases of PROM occurring between 24-31 weeks fetal prognosis is mainly influenced by gestational age at birth and fetal infectious complications[13].

Corticosteroids used to accelerate lung maturity are represented by intramuscular administration of dexamethasone and betamethasone. Other corticoid drugs (prednisolone, prednisone) do not pass the placental barrier and oral preparations of dexamethasone have significant adverse effects compared with intramuscular administration. Betamethasone is administered intramuscularly in doses of 12 mg (6 mg betamethasone acetate combined with 6mg betamethasone phosphate), 2 doses in 24 hours. Dexamethasone may be administered intramuscularly 6mg at 12 hours, 4 doses.

Tocolytic treatment in cases of PROM should be administered before the onset of uterine activity to be effective in prolonging latency. Tocolysis has no effect on latency once the uterine contractions have started. Administration of tocolytic therapy is controversial because there are no studies to evaluate the effectiveness of tocolysis versus antibiotic and corticosteroid treatment. Tocolytic therapy is indicated to postpone the birth until lung maturity is obtained with corticotherapy and in the cases in which the risk of neonatal prematurity complications is very high, in order to obtain time for transportation of the pregnant women to a superior center[14].

Tocolytic effect can be achieved by administering nonselective betasimpaticomimetics agents, magnesium sulfate or slow calcium channel blocker class drugs. Antagonist oxytocin receptor like atosiban should not be used for premature rupture of membranes, especially after 30 weeks of gestation. Nonsteroidal anti-inflammatory have tocolytic effect but can be administered up to 32 weeks of gestation due to the risk of premature closure of the ductus arteriosus. Indomethacin is preferred, a loading dose of 50 mg followed by oral administration of 25 mg every 6 hours for up to 48 hours. Fetal contraindications to tocolysis with indomethacin are represented by intrauterine growth restriction, oligohydramnios, fetal renal abnormalities, ductus arteriosus permeability dependent heart defects and twin to twin transfusion syndrome.

Although tocolytic effect is weak, magnesium sulfate administered to patients with PROM in less than 32 weeks has a neuroprotective effect on the fetus with a resulting reduction in the risk of cerebral palsy. Magnesium sulphate is given in doses of 1-2mg/hour for 24 hours, monitoring maternal signs of hypermagnesemia[15].

The retrospective study of Schucker and Mercer for expectation attitude in cases of PROM between 26-30 weeks, recorded the following maternal complications: chorioamnionitis (39.3%), abruptio placentae (3.2%), endometritis (9.9%), maternal sepsis (0.8%), maternal death (0.14%). Regarding fetal prognosis the same study reported a survival fetal rate of 45%, fetal complications being represented by fetal pulmonary hypoplasia (5.9%), respiratory distress (52%), infections (15%), necrotic enterocolitis (6.4%), and bronchopulmonary dysplasia (6.4%). Although perinatal morbidity is high, 69% of survivors have no evidence of long-term neurological complications[11].

Signs of fetal infection and chorioamnionitis must be identified and termination of pregnancy is imposed once the amniotic infection has occurred.

Therapeutic conduct in premature rupture of membranes between 24-26 weeks

The cause determining the premature rupture of membranes below 24 weeks of pregnancy has implications for prognosis prediction and in guiding therapeutic attitude. Premature rupture of membranes occurred in cases of persistent bleeding in the second trimester with a subsequent oligohydramnios due to fetal malformation has a reserved prognosis.

Cases of premature rupture of membranes below the fetal viability must benefit from couples' counseling regarding the immediate termination of pregnancy or expectant conduct. Given the extremely reserved neonatal outcome of these cases and the high rate of maternal infectious complications in conservative treatment, the decision to choose expectant conduct must be well documented. In cases in which conservative treatment risks outweigh the potential postnatal benefits, termination of pregnancy is necessary. The chosen method for termination of pregnancy depends on the obstetrical conditions, patient's preferences and experience of the obstetrician.

Conservative treatment consists of broad-spectrum antibiotics, bed rest and steroids that is administered when the fetal viability limit is reached. During this period the appearance of infection signs is monitored, abruptio placentae must be excluded and the amount of amniotic fluid and fetal lung development are evaluated weekly by ultrasound after prior assessment of fetal morphology. Where documented pulmonary hypoplasia is developed before reaching the limit of fetal viability, the termination of pregnancy is decided and explained to the patient[16].

There are 5 stages of fetal lung development: embryonic stage, pseudoglandular, canalicular and saccular. PROM during fetal previability may occur during late lung pseudoglandular development (8-16 weeks) or early canalicular phase (16-28 weeks). In pseudoglandular phase the bronchi divide forming the bronchial tree and during canalicular phase terminal bronchioles and type II pneumocyte appear. Lethal pulmonary hypoplasia rarely occurs secondary to the oligohydramnios developed after 26 weeks. Ultrasound assessment of pulmonary hypoplasia is achieved by successive measurements of chest circumference and chest area. Although ultrasound is useful in the prediction of pulmonary hypoplasia there is no parameter that has a very high sensitivity in the prediction of pulmonary hypoplasia. Currently three-dimensional ultrasound assessment of lung volume seems an encouraging parameter to identify this pathology[16,17].

Studies in the 90s, reporting cases of PROM under 25 weeks with conservative therapy show a fetal survival rate of 11.7% with a rate of chorioamnionitis of 13.1%[18].

Recent studies report a fetal survival rate of 31.6% in cases of PROM at fetal viability limit. Fetal survival rate is significantly lower in cases of PROM under 22 weeks compared to those at which the rupture of membranes occurred after 22 weeks[19].

Neonatal morbidity in these cases is represented by respiratory distress syndrome occurring in 69% of cases and pulmonary hypoplasia occurring in 19.2% of cases of survivors. Neurological complications are represented in 5% of cases by grade III-IV

intraventricular hemorrhage and in 3.1% by spastic contracture. Neonatal sepsis occurs in 5% of cases of PROM below fetal viability, in which expectative conduct was decided.

In clinical interpretation of these studies we should keep in mind that they exclude cases of PROM at the limit of fetal viability in which the conduct is the termination of the pregnancy. Also in most studies investigators stopped pursuing cases on a long term basis and it is hard to achieve a realistic interpretation between the optimistic reports that underestimate the long-term deaths occurrence and the disproportionate reporting of long-term morbidity evolution[20].

Prediction and prevention of premature rupture of membranes

Often, in cases of premature rupture of membranes, birth is necessary or inevitable. Prediction and prevention of premature rupture of membranes offers the best alternative to prevent fetal and maternal complications associated with premature births. PROM prevention involves identifying clinical markers involved in this pathology and eradicating them in the pre- or post-conceptional period.

General preconception measures consist in ceasing smoking, eating a balanced diet, solving periodontal pathology and avoiding multiple pregnancies in cases of assisted human reproduction procedures[20].

Preconceptional measures for patients who have had a previous premature birth consecutive to PROM are identifying and treating Müllerin abnormalities, correcting associated medical conditions (diabetes, hypertension), diagnosing and treating any urogenital infections.

Pediatric literature studies reveal a risk reduction of PROM and premature birth with increasing the interval between pregnancies[21].

Postconceptional, the most common known causes to be involved in PROM, urogenital infections and cervico-isthmic incompetence must be identified. One must not forget that in 50% of cases of PROM the etiological factor cannot be identified.

Identifying patients at high risk of PROM and premature birth is obtained by the recognition of the following risk factors: patients with a history of PROM, bacterial vaginosis, associated medical conditions, BMI of less than 19.8 kg/m^2, cervical canal length less than 2.5 cm, fibronectin positive test. Patients with a history of PROM may benefit from treatment with progesterone, studies showing risk reduction of recurrence of PROM by 44 to 50%[21,22].

Conclusions

Premature rupture of membranes is an important cause of increased fetal morbidity related to prematurity and fetal infection. Latency from rupture of membranes to onset of birth decreases with increasing gestational age and the risk of chorioamnionitis increases with lower gestational age at the time of membranes' rupture. Therefore adopting a conservative conduct in order to extend the latency must be made after prior documentation of lung immaturity, weighing the risks of prematurity with the risks of fetal and maternal infectious. Antenatal administration of corticosteroids, magnesium sulphate and broad-spectrum antibiotics in cases of PROM arising between 24-31 weeks reduces the risk of neonatal infection and morbidity due to prematurity. ■

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