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Review Article

Advances in the Management of Premature Rupture of the Membranes

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Abstract

Introduction: Deliveries that occur before the twenty-eighth week of gestation (or even before) are considered to be an international medical concern, based on reports from the World Health Organization (WHO). Mid-trimester preterm premature rupture of membranes (PPROM), which is known as rupture of fetal membranes before twenty-eights weeks of pregnancy, is estimated to complicate about 0.4 percent to 0.7 percent of all pregnancies and is usually linked with relatively elevated neonatal mortality rates as well as long- and short-term severe complications.

Aim of Work: In this review article, we will summarize the most recent medical literature on preterm premature rupture of membranes between eighteen and twenty-eight weeks.

Methodology: We did a systematic search for preterm premature rupture of membranes using PubMed search engine and Google Scholar search engine. All relevant studies were retrieved and discussed. We only included full articles.

Conclusions: Etiologies of the mid-trimester preterm premature rupture of membranes are considered multifactorial. The "classic preterm premature rupture of membranes" with oligo/anhydramnion is linked with a relatively shorter latency period and bad neonatal outcome when compared with similar gestational aged neonates who are delivered without the presence of an antecedent preterm premature rupture of membranes. On the other hand, the "high preterm premature rupture of membranes" syndrome is known as the presence of a defect of the chorioamniotic membranes, that is not located over the internal cervical os. The treatment of preterm premature rupture of membranes needs balancing the possible neonatal advantages following prolongation the duration of gestation with the disadvantages of developing an intra-amniotic infection and its complications for both the mother and baby.

Keywords: *Preterm Premature Rupture of Membranes; Gestation; Pregnancy; Preterm Labor*

Introduction

Deliveries that occur before the twenty-eighth week of gestation (or even before) are considered to be an international medical concern, based on reports from the World Health Organization (WHO) [1]. Mid-trimester preterm premature rupture of membranes (PPROM), which is known as rupture of fetal membranes before twenty-eights weeks of pregnancy, is estimated to complicate about 0.4 percent to 0.7 percent of all pregnancies and is usually linked with relatively elevated neonatal mortality rates as well as long- and short-

term severe complications [2]. The immediate survival of babies who are born before twenty-eight weeks of pregnancy has significantly improved through the last years; nevertheless, extreme preterm delivery is still usually linked to later neonatal mortality before one month of age [3]. It is estimated that about forty percent of very preterm babies, who survive the first stay in the neonatal intensive care unit, will die later during next five years of their life. moreover, the long-term morbidity of those who survive will remain high throughout their lifetime. More than forty percent of surviving babies following preterm premature rupture of membranes before twenty-five weeks of pregnancy will develop bronchopulmonary dysplasia (BPD). Surviving children will also have increased risks of both physical disabilities and developmental disabilities, including developing chronic respiratory disease, neurodevelopmental or behavioral effects (including impairments of visual, hearing, and/or executive functions, global developmental delay and psychiatric/behavioral sequela) and cardiovascular conditions. Prolonged anhydramnion following preterm premature rupture of membranes is linked to a 4-fold higher risk of composite complications, including death, bronchopulmonary dysplasia, severe neurological dysfunctions, severe retinopathy, when compared to an age-adjusted control group of the general population [4].

In this review article, we will summarize the most recent medical literature on preterm premature rupture of membranes between eighteen and twenty-eight weeks. We will also summarize data regarding the etiology of preterm premature rupture of membranes along with diagnostic methods, and mechanisms of this condition, management plans, and maternal and neonatal outcomes.

Methodology

We did a systematic search for preterm premature rupture of membranes using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: preterm premature rupture of membranes, gestation, pregnancy, preterm labor

Etiology

Anatomy of chorioamniotic membranes

The amnion is normally composed of 5 different layers. From closest to the fetus to outside near the uterine cavity of the mother, those layers are: (1) the inner amniotic epithelial layer, closest the baby (2) the basement membrane, (3) the compact layer, (4) the fibroblast layer and (5) the intermediate layer that is in direct contact with the chorion itself. In humans as well as primates, the amnion includes no nerves or blood vessels. The amniotic epithelial cells release collagen types three and four, along with the glycoproteins laminin and fibronectin which make the attachment for the next layer of the amnion; the basement membrane. The compact layer is then formed by type one and three collagens which will be released by the closest and thickest layer of the amnion; the fibroblast (fourth) layer, that comprises mesenchymal cells and macrophages. The outer layer; the intermediate layer, is often known as the spongy layer, or the *zona spongiosa*, creates the junction between the amnion and chorion, and is comprised of type three collagen, proteoglycans and glycoproteins. The junctions between the amniotic and chorionic membranes are very fine and are not well-established; in some cases, it is even considered challenging to avoid the separation between these membranes during the preparation for the process of a microscopic examination. The chorion is usually thicker than the amnion but on the other hand, it has relatively less tensile strength. It includes a reticular layer with collagen types one, three, four, five and six, the basement membrane (which includes collagen type four, fibronectin and laminin) and trophoblast cells that has polarity that is directed toward the maternal decidua area [5].

Embryology of the chorioamniotic membranes

Prior to twelve weeks of pregnancy, the amnion is usually present within the gestational sac and is separated from the chorion by the presence of chorionic fluid and in turn encloses the baby and amniotic fluid in a different area within a sac [6]. The amnion gets its oxygen and nutritional supplements from the surrounding amniotic fluid as well as the chorionic fluid until the "fusion" of the chorionic space. These connected membranes could always be easily physically disrupted from one another, and are never actually merged, speaking from a cellular view [6]. This merging of the chorionic space usually happens between the twelfth and fourteenth weeks of pregnancy

[6] despite that the fusion can happen later in certain cases up to the fifteenth week. This presence of separation during the second trimester is usually known as the 'chorioamniotic separation' and could be observed using high resolution ultrasound. Some clinicians have reported the presence of a prolonged chorioamnion separation as an aneuploidy indicator. Chorioamniotic separation is commonly seen as an adverse event of performing fetal surgery [7]. Following delivery, the chorioamniotic membranes could be manually separated from one another.

Mechanisms of the premature rupture of the fetal membranes

Pathologic anatomical remodeling location

The most common site for rupture of amniotic membranes in preterm premature rupture of membranes is the supra cervical area (the membrane that overlies the ostium of cervical area). The amniotic membranes at this site are anatomically altered, easily disconnected and is are usually full of bacteria [8]. Previous clinical experience has demonstrated that not all patients with preterm premature rupture of membranes show this typical pattern of the rupture. We have found patients who have positive preterm premature rupture of membranes tests but have a normal amount of the amniotic fluid when performing an ultrasound. The prognosis for these patients is usually better [9]. These patients are considered to be similar to patients who experience preterm premature rupture of membranes as an adverse event of performing feto-scopic surgery. These patients might do better than typical preterm premature rupture of membranes patients as the underlying etiology is physical disruption of the membranes without the presence of linked inflammatory and/or infectious etiology that is seen with typical preterm premature rupture of membranes.

Altered membrane morphology

preterm premature rupture of membranes is linked to the presence of significant swelling and disruption of the collagen network within all of the compact, fibroblast and spongy layers. The enzymes which have been demonstrated in the physiology of membrane rupture include MMP-1, MMP-8, MMP-9, with several studies that support this in which the levels of theses enzymes in the amniotic fluid have been assessed with immunoassays as well as enzymatic methods. Matrix metalloproteinases (MMP), or collagenases, degrade interstitial collagens, working preferentially on collagen type one. Maymon., *et al*. published a manuscript where they described that preterm premature rupture of membranes (in both, the presence or absence of an infection) was linked to higher levels of MMP-1 in the amniotic fluid MMP-1 levels [10]. Spontaneous rupture of the membranes in preterm pregnancies, but not in term pregnancies, was found to be linked with increased amniotic fluid levels of MMP-8 [11].

On the other hand, Vadillo-Ortega., *et al*. proposed that some cases may involve activation of the MMP-9 enzyme, which is a 92-kDa type four collagenase. Athayde., *et al*. also concluded that patients who have preterm premature rupture of membranes showed higher levels of MMP-9 when compared to those with preterm labor with intact membranes, who were delivered on time. Females who have microbial invasion of the amniotic cavity showed significantly higher median MMP-9 levels when compared to those without microbial invasion despite their membrane status (preterm labor: 54.5 ng/milliliter, versus less than 0.4 ng/milliliter and in preterm premature rupture of membranes patients 179. 8 ng/milliliter, versus 7.6 ng/milliliter, P was less than 0.001) [12]. Maymon., *et al*. also showed that microbial invasion of the amniotic cavity in females who have preterm premature rupture of membranes was linked to a significant increase in the levels of the active forms of the MMP-9 enzyme and a reduction in the levels of the active forms of the MMP-2 enzyme [13]. premature rupture of membranes is also correlated with elevated levels of neutrophil elastase in the amniotic fluid levels of neutrophil elastase and with decreased levels of secretory leukocyte protease inhibitor [14].

In patients who have only one of the membranes is disrupted, it is relatively challenging to be able to distinguish from the "high-preterm premature rupture of membranes" with non-diminished amount of amniotic fluid, specifically if the preterm premature rupture of membranes investigations are positive. We propose that such "pre-preterm premature rupture of membranes" situations comprise a significant percentage of patients with the wrong diagnosis of "high- preterm premature rupture of membranes" combined with normal amount of amniotic fluid. It is considered to be possible that in some cases with pre- preterm premature rupture of membranes without

any signs of the presence of an infection, the "aggressive" interventions that include systemic antibiotic therapy and hospital admission until labor, can be avoided without any complications [14].

Complications of invasive procedures and feto-scopic surgeries

Leakage of the amniotic fluid following performing amniocentesis or following feto-scopic surgery [15] proposes that in some cases the premature rupture of membranes can have two individual subtypes: (a) "Typical premature rupture of membranes" in the supra-cervical area with anhydramnion. In some cases, the typical premature rupture of membranes can be stimulated by the high premature rupture of membranes with leakage of the amniotic fluid causing injuries to the cervical mucus plug. (b) "High premature rupture of membranes" includes patients who have a membrane defect remote from the internal cervical os with a normal amount of the amniotic fluid and a better neonatal outcome (with or without a positive premature rupture of membranes test) and high premature rupture of membranes with decreased amounts of amniotic fluid volume because of the presence of a leakage of amniotic fluid (positive premature rupture of membranes test). In patients who have "high premature rupture of membranes" the amnion, overlying the cervix can be intact and the development of ascending infections is considered to be less likely, thus the risk of chorioamnionitis and fetal inflammatory response syndrome (FIRS) is not substantially elevated. Feto-scopy along with using a relatively huge sheath for the optic and operative canals and the caused defect in the chorioamniotic membranes, that persists until labor [15].

Inflammation

Histological chorioamnionitis generally complicates about fifty percent of all cases of premature rupture of membranes that happen before thirty-four weeks of pregnancy [15]. Yu., *et al*. previously published a report of gestations with premature rupture of membranes that happened before thirty-four weeks and noticed the presence of a rate of chorioamnionitis that reached eighteen percent. The latency period was more than seven days only in about twenty-four percent of patients [16].

Microbial involvement

In their paper, Romero., *et al*. concluded that fetal inflammatory response syndrome (which is known as the presence of fetal plasma IL-6 levels that are more than eleven pg/mL) was present in twenty percent (nineteen out of ninety-five cases) of patients with preterm labor and intact membranes and in about thirty-nine percent (fifteen out of thirty-nine of cases) of patients with premature rupture of membranes [17]. The frequency of microorganisms-positive cultures of amniotic fluid cultures was about twenty-two percent (ninety-nine out of 134 cases). The presence of inflammatory response syndrome was correlated with a substantial elevation in the fetal plasma levels of TNF-R1 and TNF-R2 [17]. The authors proposed that microbial products and cytokines secreted during the fetal inflammatory response syndrome might be the cause of the higher availability of soluble TNF receptors, because endotoxin and TNF-α use stimulates the shedding of soluble TNF-α receptors. The alterations in fetal plasma levels of soluble TNF-α receptors can be associated with the development of a systemic inflammatory response syndrome rather than the colonization of the amniotic cavity with microorganisms [17].

In another study, Kacerovsky., *et al*. showed that the detection of non-*Lactobacillus* bacteria in the cervical microbial community of premature rupture of membranes patients, was correlated with a significant cervical inflammatory response and higher rates of microbial invasion of the amniotic cavity. Both, microbial invasion and histological chorioamnionitis, represent a premature rupture of membranes subtype with significant inflammation [18]. The earlier the gestational age at premature rupture of membranes, the higher is the possibility of the presence microbial associated and sterile intra-amniotic inflammation.

The bacterial community that is present in the amniotic cavity can be different from those, detected in the cervical culture. Baldwin., *et al*. showed, that the placental microbiome of premature rupture of membranes patients had high individual variations and weak association with the vaginal microbiome of the mother [19]. The authors were able to detect the common pathogens including *Prevotella* spp. and *Peptoniphilus* spp. in patients with premature rupture of membranes. The antibiotic management, given for patients with premature rupture of membranes, did not eradicate these pathogenic bacteria until labor, as did the deficiency in *Lactobacilli* species.

Inflammatory mediators (IMs)

IInflammatory mediators have a causative mechanism in the disruption of FM integrity and in stimulating the contractility of the uterus. They are normally released as a part of the physiologic maternal defense mechanism in response to the pathogens' invasion. Reactive oxygen species and Inflammatory mediators, such as prostaglandins, cytokines and proteinases have a significant role in the FM thinning and apoptosis [20]. Apoptosis then follows the onset of extracellular matrix degradation, indicating that it is a result rather than a cause of FM disruption [20].

Among patients who have chorioamnionitis, apoptotic amniotic epithelial cells are usually attached to granulocytes, indicating that the immune response may predispose to apoptosis in the FM [21]. In addition, Dutta., *et al*. evaluated the damage of DNA in patients who have premature rupture of membranes and concluded the presence of elevated count of cells that show DNA damage, p38 MAPK activation, and manifestations of senescence [22]. The inflammatory response that is stimulated in these patients is considered to be secondary to the production of cytokines. The inflammatory mediators and production of matrix degrading enzymes including matrix metallo-proteinases, elastases, catepsins and TNFs are implicated in pathophysiologies that are responsible for the development of premature rupture of membranes during the second trimester of pregnancy [23].

Mechanical stretch

Chorioamniotic membranes at term have a relatively weak area in their region that overlies the cervix, that shows features of higher rates of collagen remodeling and apoptosis. Preterm FM also show a weak zone but are generally stronger overall, than term FM [24]. Preterm contractions of the uterus or over distention of the fetal membranes in polyhydramnios conditions elevate the risks of developing premature rupture of membranes [23]. These developmental events, causing early uterine contractions, can be different from those, causing preterm rupture of the membranes [24].

Kumar., *et al*. demonstrated that the presence of stretch forces alone cannot entirely be responsible for causing FM weakening, as the force that is generated by uterine contractions are not sufficient to cause rupture of the FM without leading to the development of a pre-weakening status [24]. In their study, Moore., *et al*. demonstrated that fibulins one, three and five, which are involved in creating bridges in the extracellular matrix, were colocalized with major and demonstrated reduced abundance in the amniotic component of the FM weak area [25]. A potential mechanism for this significantly higher degradation rate of FM collagen can be the presence of enzymatic breakdown of certain collagen molecules leading to the remaining stress that is present in the tissue, which has to be turned into neighboring molecules, that might later rupture. If this is a generally common event to occur, fast break down of the collagen molecules can consequently cause a significant breakdown of the tissue [25]. Therefore, is it likely that mechanical stress might stimulate weakening of the collagen molecules by injuring the collagen molecules that organize collagen Type one, such as decorin, biglycan, the fibulin family.

Conclusions

MMid-trimester preterm premature rupture of membranes (PPROM), which is defined as the rupture of the fetal membranes before twenty-eight weeks of pregnancy, is an adverse event that can occur in about 0.4 percent to 0.7 percent of all gestations. This medical condition is generally correlated with a significantly high rates of neonatal mortality along with a higher risk of long-term and short-term severe neonatal morbidity. Etiologies of the mid-trimester preterm premature rupture of membranes are considered multifactorial. Changes in the membrane morphology including significant swelling and dysfunctional collagen network are observed in cases of preterm premature rupture of membranes and can be stimulated by the secretion of bacterial products or/and the presence of pro-inflammatory cytokines. The "classic preterm premature rupture of membranes" with oligo/anhydramnion is linked with a relatively shorter latency period and bad neonatal outcome when compared with similar gestational aged neonates who are delivered without the presence of an antecedent preterm premature rupture of membranes. On the other hand, the "high preterm premature rupture of membranes" syndrome is known as the presence of a defect of the chorioamniotic membranes, that is not located over the internal cervical os. It might be linked to either a physiological or decreased amount of amniotic fluid. Confirming a diagnosis of preterm premature rupture of membranes is

typically made by detecting a nitrazine positive, fern positive watery leakage out of the cervical canal seen during in *specula* investigation. Other more sophisticated diagnostic investigations include the use of the vaginal swab assay for placental alpha macroglobulin-1 test. The treatment of preterm premature rupture of membranes needs balancing the possible neonatal advantages following prolongation the duration of gestation with the disadvantages of developing an intra-amniotic infection and its complications for both the mother and baby.

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