Chapter 8
Premature Rupture of Membranes and Oxidative Stress

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Abstract Premature rupture of membranes (PROM) is rupture of the chorioamniotic membranes before the onset of labor. The chorioamniotic sac requires a balance between collagen formation and enzymatic collagenolytic activity expressed in the fetal membrane. The amniotic membrane is a complex tissue in which collagen is fundamental for mechanical integrity and stress tolerance. Membrane rupture is associated with biochemical disturbances between collagen produced by fibroblasts and fetal membranes. An association exists between PROM and oxidative stress (OS) in pregnancy. Reactive oxygen species (ROS), which are unstable molecules produced in the body, may be the reason for the collagen damage. OS produced by augmented ROS production debilitates the collagen’s elasticity and strength, leading to PROM. Although antioxidants act as defense agents against oxidation, they have not been found to be protective against ROS and subsequent OS damage in PROM.

Keywords Premature rupture of membranes · Chorioamniotic membranes · Oxidative stress · Enzymatic collagenolytic activity expressed · Fetal membrane
8.1 Introduction

Parturition is determined by ripening of the cervix, augmented contractility of the myometrium, and positive signaling of the maternal decidua and the chorioamniotic membranes. Activation of genes involved in inflammatory activities promotes the chorioamniotic membrane to undergo complex biochemical changes [1]. Premature rupture of membranes (PROM) is defined as rupture of membranes before the onset of labor and membrane rupture that takes place before 37 weeks of gestation is known as preterm PROM [2]. At term, weakening of the membranes occurs from physiologic changes in association with shearing forces created by uterine contractions [3, 4]. Normal rupture of membranes at term is thought to begin at a specific weakened para-cervical region which forms late in gestation due to collagen disruption [5]. Intraamniotic infection is commonly associated with preterm PROM, especially if it occurs at an earlier gestational age [2]. Low socioeconomic status, second- and third-trimester bleeding, low body mass index less than 19.8, nutritional deficiencies of copper and ascorbic acid, connective tissue disorders, maternal cigarette smoking, pulmonary disease in pregnancy, uterine overdistention, and amniocentesis are some of the risk factors associated with PROM occurrence [6, 7].

The amnion is an avascular entity that depends on the amniotic fluid for its stability and may be involved in the pathogenesis of PROM [8]. The chorioamniotic sac requires a balance between collagen formation by fibroblasts and the collagenolytic activity by enzymes expressed in the fetal membrane [9]. Membrane rupture is associated with biochemical disturbances between collagen produced by fibroblasts and fetal membranes [9]. The elasticity and strength of fetal membranes is primary determined by collagen. Reduced concentrations of it or altered cross-linked organization may contribute to PROM [10].

MnSOD formation. MnSOD is a member of an iron/manganese superoxide dismutase family which is located in the mitochondria and inhibits reactive oxygen species (ROS) produced by oxidative phosphorylation [1]. A moderate increase in ROS can stimulate cell growth and proliferation, while an excessive ROS accumulation will lead to cellular injury, such as damage to DNA, protein, and lipid membrane. ROS enhance NF-κB and promote the expression of cyclooxygenase-2 (COX-2), which upregulates the inflammatory pathway and the propagation of labor [1]. These inflammatory processes may lead to increased formation of ROS and subsequent oxidative stress (OS). OS occurs when the production of ROS exceeds the endogenous antioxidant defense. On the contrary, MnSOD may be activated by inflammatory processes, which in turn downregulates OS and inflammation by inhibiting NF-κB and mitogen activated protein pathways (MAPK) [1].
8.2 Chorioamniotic Membrane: What is it Made of?

The amnion is a single layer of non-ciliated cuboidal cells with its outermost part near the amniotic fluid. Beneath the amnion there is a layer that consists of loosely packed fibrils and where the chorion, which composed of reticular fibers, a basement membrane, and the trophoblast cells, is found. Under the chorion is the maternal decidual layer, which consists of epithelial cells that allow the separation of the chorioamnion from the endometrial and myometrial layers of the uterus [11].

The amnion originates its strength from collagen. At least five (types I, III, IV, V, and VI) types of collagen are encountered in the chorioamnion which are organized in triple helices [10]. Collagen strength, which is primarily attributed to collagen I, is derived from hydroxyproline and hydroxylysine bridges around the helix. The reticular layers contain collagen I, III, IV, V, and VI. The chorionic basement is composed of collagen IV and the chorion has types IV and V [12].

The chorioamnion is a biologically active membrane whose collagenolytic enzyme is susceptible to ROS proliferation [13].

8.3 Premature Rupture of Membranes, Oxidative Stress, and Antioxidants

In the normal physiological capacity, a delicate balance exists at the molecular level between oxidants and antioxidants. ROS may play a role in the collagen damage in the chorioamniotic sac leading to tearing [9]. OS occurs when the production of reactive oxygen species exceeds the antioxidant defense. OS may altercate the elasticity and strength of collagen and promote PROM [10, 14]. Isoprostanones (F2-IP) can be used to a marker of OS [15], especially of lipid peroxidation [9]. They are prostaglandin-like products produced by free radical catalyzed nonenzymatic peroxidation of arachidonic acid [9]. Peroxidation decreases, disrupts membrane barrier function and lowers its fluidity [16]. F2-IP levels in the amniotic fluid at 15–18 weeks gestations are a predictor of PROM in preterm deliveries [9].

The antioxidants play a role in the protection of the chorioamniotic sac from oxidant damage [17–20]. Vitamin C (ascorbic acid) is a known redox catalyst, which has the ability to reduce and neutralize ROS. It plays a primordial role in the formation of collagen triple helix and the fortification of collagen cross-links[5]. Vitamin E is a lipid soluble vitamin with antioxidant activity. It constitutes of eight tocopherols and tocotrienols. α-Tocopherol is considered to play a central role due to its capability to react with lipid radicals produced during lipid peroxidation reaction. In vitro, Vitamins C and E have been successful in the protection of the amnion and chorion from damage induced by ROS [8]. Mechanisms have proposed that Vitamin C may salvage oxygen species in the amniotic fluid and Vitamin E may prevent lipid peroxidation [8]. In contrast to the reports implying a
protective action, Bolisetty et al. [20] found that antioxidant vitamins, especially vitamin E, diminish markers of OS at birth. Mathews et al. [8] found no evidence to support the hypothesis that antioxidants against PROM. Finally, Mercer et al. [5] postulated that antioxidant treatment with Vitamin C and E may inhibit ROS formation and resultant fetal membrane weakening. Two studies were conducted, one in vitro and the other in vivo, and concluded that neither antioxidants were effective in the prevention of PROM.

Superoxide dismutases are antioxidant enzymes that protect cells against ROS and damage [21–23]. There are four classes that differ by, their protein configuration, the intra- or extracellular localization and the active metal ions (Cu/Zn, Mn, Fe, or Ni) in their catalytic centers [21]. In humans, MnSOD is encoded by SOD2, which is synthesized in the cytosol and imported into the mitochondrial matrix [1]. Than et al. [1] showed MnSOD mRNA expression in the fetal membranes and in chorioamnionitis of PROM suggesting an antioxidant mechanism to counteract the inflammatory process in the chorioamniotic membranes.

8.4 Conclusion

PROM is characterized by reduced collagen concentrations, altered collagen cross-link profiles, and increased concentrations of biomarkers of oxidative damage. In the amniotic membrane, collagen is primordial for mechanical integrity and stress tolerance. The OS that occurs during pregnancy increases the risk for PROM that is caused by changes in collagen integrity. In the future, trials should focus on determining if supplementation with antioxidants could protect the fetal membranes from premature rupture.

References