Seminars in Perinatology ▮ (2017) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

Preterm prelabor rupture of the membranes: A disease of the fetal membranes

Ramkumar Menon, MS, PhD, and Lauren S. Richardson, BS*

Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, 301 University Blvd, MRB, Room 11.138, Galveston, TX 77555-1062

ARTICLE INFO

Keywords:
Fetal signals
Parturition
Exosomes
Biomarker
Aging
Fetal membranes
Amniochorion

ABSTRACT

Preterm prelabor rupture of the membranes (pPROM) remains a significant obstetric problem that affects 3–4% of all pregnancies and precedes 40–50% of all preterm births. pPROM arises from complex, multifaceted pathways. In this review, we summarize some old concepts and introduce some novel theories related to pPROM pathophysiology. Specifically, we introduce the concept that pPROM is a disease of the fetal membranes where inflammation–oxidative stress axis plays a major role in producing pathways that can lead to membrane weakening through a variety of processes. In addition, we report microfractures in fetal membranes that are likely sites of tissue remodeling during gestation; however, increase in number and morphometry (width and depth) of these microfractures in pPROM membranes suggests reduced remodeling capacity of membranes. Microfractures can act as channels for amniotic fluid leak, and inflammatory cell and microbial migration. Further studies on senescence activation and microfracture formation and their role in maintaining membrane homeostasis are needed to fill the knowledge gaps in our understanding of pPROM as well as provide better screening (biomarker and imaging based) tools for predicting women at high risk for pPROM and subsequent preterm birth.

Introduction

Preterm prelabor rupture of the membranes (pPROM) is defined as rupture of the fetal membranes prior to 37 weeks of completed gestation. This significant obstetric problem occurs in about 3–4% of all pregnancies and is directly antecedent to 40–50% of all preterm births.[1,2] Since about 560,000 babies are born prematurely each year in the United States (~12.0% of all births), this correlates to about 150,000 spontaneous preterm births (sPTBs) that are complicated by pPROM.[3] The number of pPROM cases exceeds that of preeclampsia and gestational diabetes and other iatrogenic preterm births. In addition, neonatal mortality and morbidities are higher in pPROM group than any other subclasses of preterm births. Yet, pPROM is an often-ignored and understudied adverse outcome of pregnancy. Despite remarkable improvements in prenatal care over the past three decades, rates of pPROM and subsequent preterm delivery have worsened.[4]

While several tests are available to confirm a diagnosis of pPROM post-facto (e.g., pooling, fern tests, nitrazine, and Amnisure), no method to reliably predict pPROM is available. This dilemma is mostly attributable to the fact that precise causes or risk factors are unknown and pathways resulting in pPROM have only recently been delineated.[4] Empirical

* *Corresponding author.*
E-mail address: Ram.menon@utmb.edu (R. Menon).

http://dx.doi.org/10.1053/j.semperi.2017.07.012
0146-0005/

treatment approaches that ignore the complexity and heterogeneity of pPROM pathophysiology have to date been futile.[5] Proper diagnosis and management of pPROM is likely to require thorough investigation of specific exposure-induced pathophysiologic pathways and the development of biomolecular markers that can predict pPROM.

pPROM arises from complex, multifaceted pathways. Several epidemiological and clinical factors are considered precursors to pPROM. These include maternal reproductive tract infections (e.g., bacterial vaginosis [BV], trichomoniasis, gonorrhea, Chlamydia, and occult chorioamnionitis), behavioral factors (e.g., cigarette smoking, substance abuse, poor nutritional status, and coitus during pregnancy), obstetric complications (e.g., multiple gestation, polyhydramnios, incompetent cervix, gestational bleeding, prior cervical surgery, and antenatal trauma).[6–8] Environmental factors (e.g., stress and toxin exposure) and genetic predisposition also have been proposed. In addition, biochemical signals from the fetus, including endocrine signals that promote fetal membrane apoptosis, have also been implicated in the initiation of pPROM.[5–9] In this review, we summarize some old concepts and introduce some novel theories related to pPROM pathophysiology.

Fetal membranes: structure and function

Human–fetal membranes, also referred as placental membranes or amniochorionic membranes, is the inner lining of the pregnant intrauterine cavity. These fetal tissues are distinct from placenta and serves as a barrier between the fetoplacental and the maternal compartments. Fetal membranes are comprised of the amnion (innermost layer of the intraamniotic cavity) and the chorion (fetal tissue connected to maternal decidua), and are connected by collagen-rich extra-cellular matrix (ECM).[9] ECM, which is made up of fibrous proteins along with various types of collagen, provides the architectural and structural framework of the fetal membranes (Fig. 1).[9,10] The amnion is constantly bathed in amniotic fluid, signifying its importance as a primary responder to changes in the amniotic cavity. The chorion is in close proximity to maternal decidua and maintains the immune tolerance at the maternal–fetal interface.[11–14]

The amnion and chorion are fetal tissues in origin and play major roles in maintaining pregnancy by providing multilevel protection to the growing fetus. Fetal membranes accommodate constant challenges (immune, structural, mechanical, and endocrine) during pregnancy; continue to grow and mechanistically, as well as biochemically, maintains elasticity to the stretch forces experienced during fetal growth. Despite the fact that membranes overlaying the placenta and cervix face distinctly different environments and insults during pregnancy, the membranes still maintain the homeostatic balance necessary to sustain fetal growth without interruption. This companionship between the fetus and the membranes continues until term when the fetus reaches maturity and the membranes reach longevity.

Development of fetal membranes

The development of amnion and chorion begins with embryogenesis, although they do not participate directly in the formation of the embryo or fetus.[15] Like the fetus, early growth of the amnion and chorion layers is rapid and independent of each other. The formation of amniochorion as a unit structure is complete by the 12th week of gestation.[15] The composition of the membrane and its ability to produce a broad spectrum of biomarkers at different stages of gestation illustrate the possible role of the fetal membrane's influence on the growing fetus, as well as in adverse pregnancy outcomes.[10] In addition, fetal membrane cells continue to divide throughout pregnancy and its growth plateaus at term, retaining the capacity for DNA replication.[11] Lastly, the presence of stem cells in fetal membranes further depicts the likely important role of fetal membranes during in utero fetal life.[9,12–14]

pPROM: a disease of the fetal membranes

Unlike the placenta, fetal membranes are not involved in transport of nutrients or other materials. One of the major functions of fetal membranes is to protect the fetus during its growth and development in utero. Specifically, the fetal membrane functions to provide mechanical[16,17] and immune protection and acts as a barrier for microbial access.[12,18,19] This protective role is supported by the biomarkers that are produced by fetal membranes during gestation and parturition.[20] Compromise in the immune and mechanical properties of the fetal membranes allows for microbial invasion from genital tract,[21] activation of host inflammatory response leading to collagenolysis mediated mechanical disruption,[16,22–24] and membrane weakening predisposing the membranes to pPROM. Abruption associated thrombin, matrix metalloproteinase (MMP) activation and collagenolytic processes have also been reported in fetal membrane weakening and pPROM.[25] Clearly, the dysfunctional status of fetal membranes is more evident in pPROM than sPTB with no ROM. Thus, pPROM is considered as a disease of the fetal membranes and likely a separate entity from sPTB with no ROM. Current research on this disease of the fetal membranes is focused on addressing three major questions: (1) what are the initiators of proteolytic activity in the fetal membranes resulting in pPROM, (2) what are the effectors (biochemicals) of proteolysis, membrane weakening/rupture and can these biochemicals serve as markers to predict risk of pPROM, and (3) how can we reduce the risk of pPROM prior to its occurrence and minimize the impact on maternal–fetal well-being.[26]

Risk factors for pPROM

Approximately, 70% of pPROM cases are associated with intraamniotic infection (IAI), as documented by positive amniotic fluid (AF) cultures or by clinical evidence of infection.[4,27] However, it has been debated whether infection is a cause or consequence of pPROM. Histological and microbiological findings indicate that focal infection and inflammation may play a primary or secondary role in the pathogenesis of pPROM.[28] Evidence of inflammatory changes is reported to be adjacent to the putative site of membrane rupture, suggesting that bacterial infection may be an initiator of pPROM.[1] However, bacterial toxins and bacteria-derived