Review Article

Current Knowledge of Preterm Premature Rupture of Membranes

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Abstract

Preterm Premature Rupture of Membranes (PPROM) is a serious pregnancy complication that increases that risk of preterm birth. Two major factors involved in PPROM are oxidative stress and inflammation. Macrophages serve an important role in healing by clearing damaged tissue and supporting repair. MIF may influence how well macrophages perform these functions, especially during the repair process after PPROM. This review explores the important role of MIF and macrophages in the healing process of of PPROM and how they might interact. Understanding the interaction between MIF and macrophages could lead to new treatments that improve healing and preventing side effects for both mother and baby after PPROM.

Key words: Preterm, Premature rupture of membranes, Macrophages, MIF.

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Introduction

Preterm Premature Rupture of Membranes (PPROM) is the rupture of membranes during pregnancy before it reaches 37 weeks, Preterm birth affects approximately 15 million women worldwide, of which 30 % is due to preterm premature rupture of membranes.[1] PPROM cases surpass the cases of gestational hypertension, diabetes during pregnancy, and other premature deliveries cause of different medical interference. On the other hand, PPROM occurs when fetal membranes rupture prior to the beginning of labor, mostly occurring near full term.[2-3] It is a critical condition that linked to elevated risks of preterm birth & neonatal and maternal morbidity & mortality. Despite being a critical pregnancy complication, PPROM is a frequently overlooked and under-researched negative outcome of pregnancy.

Unfortunately, over the past thirty years, the incidence of PPROM and resulting preterm deliveries has increased despite advancements in prenatal care.[4] Recent research shows that macrophages play a vital role in regulating inflammation, tissue remodeling & healing within the fetal membranes. This review has ability to explore the new novel therapeutic strategies that will help to reduce preterm birth associated with PPROM.

Methodology

A comprehensive search was conducted using PubMed, PMC, Google Scholar, as well as relevant reference lists. The terms “PPROM”, “macrophages”, “MIF”, “healing process” were used in various combinations. Studies published from 1960-2024 were included.

The study was carried out in accordance with the ethical principles outlined in the 2013 Declaration of Helsinki and received approval from the ethics committee of the First Affiliated Hospital of Chongqing Medical University (Approval No. 2023-0309).

Author contributions: [1]Conceived and designed the study, participated in supervising the different phases of the study, and determined the content of the manuscript. [2,3] written the manuscript provided technical or material support and gave a critical opinion of the manuscript.
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Causes of PPROM

Approximately 30% of PPROM cases are attributed to infections in the amniotic fluid [AF], while 70% are not related to infections.[5] Inflammation & oxidative stress [OS] are significant factors in the development of PPROM that can weaken the membranes in different ways.

Inflammatory changes have been observed very close to the suspected area of membrane rupture, which indicates that the onset of PPROM might have strong connections with a bacterial infection.[1] However, bacterial toxins and enzymes that break down the matrix, have been excluded as the leading causes of PPROM for several reasons:① the level of bacterial toxins needed to damage isolated membranes are not present in AF; ②PPROM occurs in women experiencing intra-amniotic infection (IAI) caused by micro-organisms that do not release proteases; ③ most bacterial enzymes that degrade the matrix lack the ability to specifically break down human extracellular matrix collagens; ④ In numerous cases PPROM observed despite successful antibacterial treatment for periodontal disease, bacterial vaginosis and IAI.[6-8]

A normal pregnancy, like other normal physiological conditions, maintains a stable equilibrium between reactive oxygen species and antioxidants.[9-13] OS enhances placental mitochondrial activity and reactive oxygen species (ROS) release when the fetoplacental unit has high energy needs, such as during pregnancies at high altitudes. This results in a disrupted redox balance.[14] Behavioral risks factors for PPROM, such as cigarette smoking, promote the generation of superoxide, nitric oxide, and hydroxyl ion, which can impair the collagen matrix and diminish antioxidant defenses.[15-22] ROS degradation particularly affects collagen, making it highly vulnerable. Superoxide has been shown to induce the breakdown of fibrillar collagen into 4-hydroxyproline in vitro.[23] Collagen breaking enzymes in the chorioamniotic membranes are also vulnerable to activation by ROS.[24.] For example, glutathione precursor N-acetylcysteine (NAC) or superoxide dismutase (sod) can both suppress matrix metalloproteinase-9 (MMP9) activity. Lappas and colleagues has demonstrated the suppression of MMP9 and other markers of inflammation by NAC.[25] NAC works by blocking an NF-κB-activated pathway, which in turn reduces the metabolism of phospholipid, the release of particular pro-inflammatory cytokine and proteolytic activity peaks within human fetal membranes.[25]

Fetal membrane apoptosis was identified as a pathological process linked to PPROM more than ten years ago.[26-31] The conclusion provided additional support for this discovery that apoptotic components are commonly found in membranes from Protease activity and pro-inflammatory cytokine release in human fetal membranes.[27] without rupture of membranes (ROM). Many pro-apoptotic factors which are typically not present in membranes taken after sPTB with intact membranes during PPROM are triggered by infections and other endotoxins.[29,32,33] A typical DNA fragmentation pattern, commonly has been noted, accompanied by apoptosis, to fetal membranes which have been collected from women with PPROM. Oxidative stress also leads to DNA fragmentation in fetal membrane cells.[34] Since inflammatory mediators have the ability to cause different types of cell death, based on their exposure time and concentration, it is likely that PPROM involves multiple forms of cell death.

Maternal stress or under-nutrition, smoking, intrauterine bleeding, oxidative stress and medical procedures like amniocentesis or fetoscopy are the factors that cause PPROM that are not linked to infection. According to Romero et al., intra-amniotic inflammation presents in 37% of preterm labor cases before 37 weeks of gestation. Remarkably, infection induced inflammation was present in just 11% of cases, in contrast, non-infectious induced inflammation, without bacterial presence, was observed in 26%.[35]

Recent studies suggest that PPROM can be linked with non-infectious induced inflammation in fetal membranes that resemble infection but without any microbial presence confirmed by culture or molecular methods.[35]

The above evidence emphasizes that oxidative stress and inflammation are key factors in PPROM. At term, about 8% of pregnancies that lead to serious complications are affected by PPROM. About 1% of all deliveries are complicated by PPROM and it is twice likely in PPROM African Americans.[36]

Fetal membranes: Structure and function

The lining of the pregnant uterus is made up of fetal membranes commonly known as placental membranes or amniochronic membranes of human. The fetal-placental and the maternal compartments are separated by these fetal membrane tissues that are different from placenta. Fetal membranes consist of the amnion, the innermost layer of the intra-amniotic cavity and the chorion, fetal tissue attached to maternal decidua. These

layers are interconnected by an extra cellular matrix (ECM) that is rich in collagen.[37] The structural foundation of the fetal membranes are formed by the ECM, consisting of fibrous proteins and various collagen types (Figure 1).[37-38] The inner most layer amnion, continuously immersed in amniotic fluid, plays a crucial role as the main agent to changes in the amniotic cavity. The chorion, positioned near the maternal decidua, helps maintain immune tolerance at the maternal-fetal interface.[39-42]

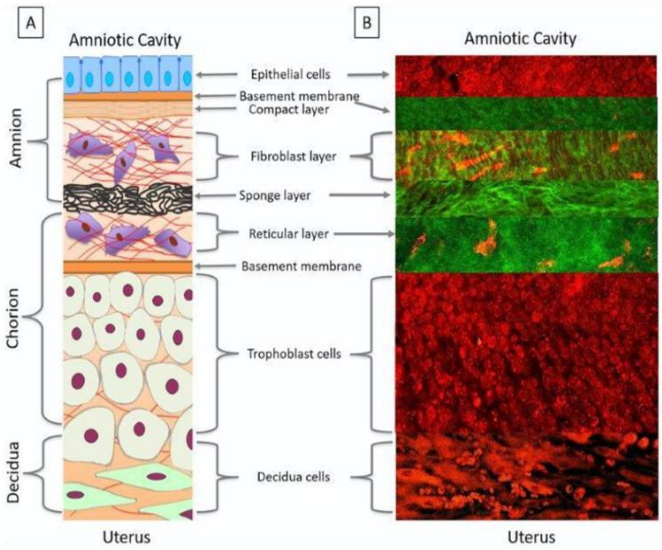

Figure 1 Structural Foundation of the fetal membrane

Pathology of PPROM

Various factors that contribute to weakening of membrane can cause the rupture of membranes. These factors include elevated levels of local cytokines, a disrupted balance between matrix metalloproteinases (MMPs) and tissue inhibitors, heightened activity of collagenase and protease, as well as other contributing factors that may increase intrauterine pressure.[36]

Collagenlysis, extracellular matrix (ECM) breakdown and fatal membranes rupture:

The disintegration of the ECM rich in collagen that joins the amnion and chorion layers of the fetal membranes is a crucial step in the onset of rupture of membranes (ROM).[43-48] Several MMPs are involves in the degradation process, each targeting specific collagen types for turnover. The following occurs via mechanisms like transcriptions, translation, and post-translational modifications or by their endogenous inhibitors, the tissue specific inhibitors of metalloproteinases (TIMPs). can modulate the MMP activity in fetal membranes.[49-50] A balanced MMP/TIMP system is essential for both during typical labor and in cases of PPROM. While the exact disruption of this balance in PPROM remains unclear, proteases linked to inflammation or infection can initiate endogenous MMPs in human fetal membranes, resulting to collagen degradation and weakening of membrane.[51-57]

In summary, previous researches have separately investigated the role of inflammation, infection, collagen breaking enzymes and apoptosis in PPROM, with the assumption of identifying pathways associated with specific risk factors would help identify the triggers and mediators of PPROM in individual cases. No reliable biomarkers, or significant improvements, in preventing PPROM and sPTB, have resulted from these studies despite these efforts.

Healing of PPROM:

The process of healing in adult tissues namely classified into the following steps: ① hemostasis ② inflammation ③ migration & proliferation ④ resolution and remodeling.[58] On the other hand, fetal tissue healing [58,] characterized by minimal inflammation, no vascularization, and no formation of granulation tissue is a simpler process. These characteristics allow for rapid and scar less healing.[59]

The injury to human fetal membrane creates an inflammatory response that begin healing process of the fetal membrane (as depicted in Figure 2).[60-61] In the context of wound healing, neutrophils are the initial immune cells to reach the injury place during inflammation, migrating from the injured blood vessels.

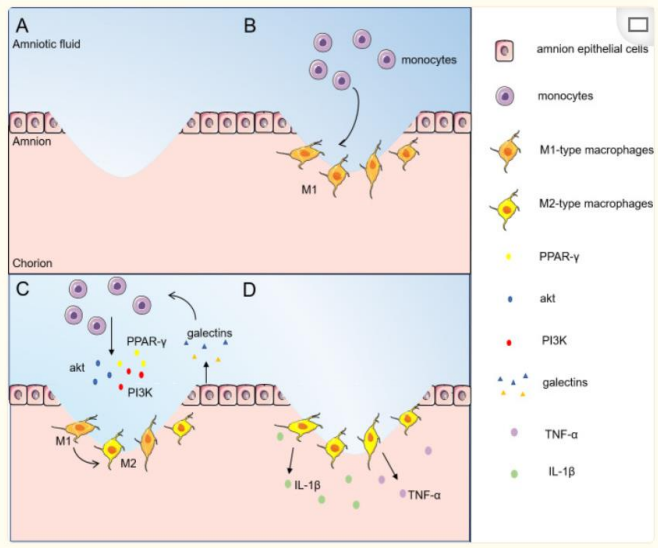

Figure 2. Inflammatory responses begin healing of amnion.

In contrast to neutrophils, monocytes are typically attracting to wounds at a later stage. Upon arrival, they differentiate into macrophages, that engage in removal of debris and dying neutrophils through phagocytosis. [58] Interestingly, studies have shown that macrophages are the only main immune cells that gather around amniotic membranes that have ruptured without infection. In contrast, neutrophils migration is rarely observed during epidermal wound healing process in adult skin, where the flow of neutrophils is seldom noticed.[62] Such could be due to the absence of infection stimuli together with the lack of infection and inflammatory stimulus. Macrophages type 2 (M2), which are found in high numbers, migrate from the amniotic cavity to the site of injury and secrete healing cytokines such as tumor necrosis factor-alpha (TNF-α) and interlukin-1 beta (IL-1β), which moderate the response for injury and inflammation of the fetal membranes.[62] Consequently, M2 macrophages might be vital in the intimate membranes' inflammatory response.

Animal models for healing of membrane

Interestingly, the initial histological researches of the regeneration process in embryonic membranes were performed using rats. According to Sopher's research [63], puncturing gestational sacs of rat on the 15th day of pregnancy using a 21-gauge needle led to a significant proliferation in mesenchymal cells of amnion layer within just 24 hours. In addition, Mogami's demonstrated that small size of ruptures (0.47 mm) created during the second trimester, using an aseptic puncture model in mice and culturing primary human amnion cells, were capable of healing successfully.[62]

Additionally, in a notable case, collagen transplantation was performed on patients Following early PPROM which occurred spontaneously at 16.5 weeks of pregnancy, a male infant was delivered successfully. at 30 weeks and 3 days gestation with an Apgar score of 6-7. The male infants grew up to become healthy and active adults.[64] However, throughout the entire gestational period, the interactions between the sealant

Table I: Preclinical studies of fetal membranes healing.

Author name	Year	Experiment design	Highlights	Title of references
Sopher D	1972	Rat/in vivo	21G needles: caused the amnion mesenchymal cells on the edge of the amnion to multiply rapidly within 24 h.	Effects of injury on rat fetal membranes.[63]
R Devlieg-er	2002	fetoscopic/in vivo	Fetoscopic access port sites plugging by collagen in sheep leads to the effective sealing of fetal membranes functionally.	Matrix metalloproteinases-2 and -9, along with their natural tissue inhibitors, play a key role in tissue remodeling following the sealing of fetal membranes. This process has been studied in a sheep model to understand the effects of fetoscopic surgery.[66]
Nicole Ochsenbein-Kölble	2003	AEC Culture/in vitro	The cultures remained viable for 14 days, demonstrating robust survival. An increase in cell density, survival rates, and proliferation activity was also observed.	Encouraging the growth of human amnion epithelial and mesenchymal cells to explore potential ways to repair membranes in the future.[67]
Haruta Mogami	2017	Mouse/in vivo	Small tears in the fetal membrane typically healed within 72 hours, while larger ruptures had a much lower healing rate, with only 40% closing successfully.	Exploring Solutions for Early Pregnancy Challenges.[62]
Haruta Mogami	2018	Mouse/ in vivo	Based on the information provided, 90% of the wounds treated with collagen type 1 injections healed, whereas 40% of the wounds treated with PBS showed the same results. This was done using the 26- or 20-gauge needles.	Collagen Type 1 Plays a Key Role in the Healing Process of Ruptured Fetal Membranes.[64]
Lauren Richards-on	2018	AEC Culture/in vitro	Healing progress: self-renewal, transition, migration, and proliferation.	The growth, movement, and changes in behavior of human amnion cells reveal their metastatic state.[68]
Ah-young Lee	2020	amniotic pore culture/in vitro	20 G needles: 100% healed; 26G needles:40% healed.	The simulation of the amniotic membrane rupture before term shows a spontaneous recuperative process of the human amnion [69]

and the membranes remained limited in vivo, with only a small number of explants examined. Moreover, the prolonged healing process of cultured fetal membrane explants my lead to deteriorating conditions in vitro, potentially compromising their capacity for repair over time. [65]

Macrophage involvement in wound repairing:

The process of wound healing is facilitated by macrophages, which can be divided into two categories [69]: Conversely activated macrophages (M2 macrophages) and similarly activated macrophages (M1 macrophages).[68] M2 macrophages perform a crucial function in facilitating wound healing, which produce anti-inflammatory cytokines and express tissue repair markers.[67]

Furthermore, the recruitment of macrophages to injury sites is a remarkable aspect of fetal tissue healing. Circulating monocytes are differentiate into tissue macrophages at the injury sited when they migrate there, while tissue-resident macrophages also perform a crucial function in the wound repairing process.[66] They secrete the growth factors, transforming growth factor (TGF-β) and platelet derived growth factors (PDGF), which enhance activation in the injured epidermis and fibroblasts cells. Constant tissue damage prevents excessive tissue destruction. TGF-β that are proficient in tissue contraction and TIMPs release, mask MMPs, preventing excessive tissue degeneration, serve a pivotal function in the alteration of fibroblasts into myofibroblasts. In conjunction with macrophages, myofibroblasts aid in injury rehabilitation by secreting collagen and performing tissue restoration. Macrophages start the reorganization of damaged tissue after releasing MMPs and TIMPs. Macrophages also phagocytose the damaged area eradicating the extracellular matrix (ECM) in the process to cleanse the wound.[68]

Macrophages and PPROM Membrane Healing:

Fetal membranes release danger signals like DAMPs (danger-associated molecular patterns) and pro-inflammatory cytokines following PPROM damage. These signals activate macrophages, prompting them to migrate to the injury site guided by chemokines and other inflammatory mediators.[66,70] Upon arrival, macrophages take on several essential tasks. They engulf and eliminate cellular debris, pathogens, and foreign material present in the amniotic fluid, preventing further infection and tissue damage.[71] It is the macrophages that are orchestrating the inflammatory response. To attract other immune cells and help fight infection, they secrete pro inflammatory cytokines, such as the IL-1β, TNF-α and interleukin-6 (IL-6). Unfortunately, this strategy can also cause extensive tissue injuries. Consequently, these macrophages produce cytokines that suppress inflammation: interleukin-10 (IL-10), and transforming growth factor beta (TGB-β).[72,73] Macrophages help in the repair of tissues by secreting growth factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) which are quite fascinating. These growth factors promote blood vessel formation, collagen deposition, and overall tissue regeneration within the fetal membranes.[74] As healing progresses, macrophages adopt a reparative phenotype. They decrease inflammation and promote the return of balance (homeostasis) within the fetal membranes.[69]

In conclusion, macrophages are essential for healing after PPROM. They act as a defense system, clearing debris and pathogens, regulating inflammation, promoting tissue repair, and ultimately restoring fetal membranes health.

Macrophage Migration Inhibitory Factor (MIF) and PPROM Healing:

The protective barrier surrounding the fetus is disrupted by PPROM, posing a significant risk for complications. Immune cells such as macrophages that are crucial for healing, play a vital role in PPROM recovery. Yet there are many other considerations featuring MIF which could influence their potency.[75] MIF plays a dual role in human body. It can cause break down and weakening of the fetal membranes by causing inflammation or it can repair and regulate the inflammatory responses and can promote tissue repairing. As a pro-inflammatory cytokine, the production of MIF in chorioamniotic membranes or in AF increases in the presence of any infection or inflammatory response which can lead to the inflammation surge. It causes the weakening and break down of the fetal membranes through the activation of MMPs and other enzymes that can lead to the rupture of membranes.[76] MIF also plays a major role in wound or injury healing. An experiment was performed on mice in 2005, that explained the local application of MIF has repaired wound healing, promoting pro-collagen production than MIF deficient mice.[77] In the framework of PPROM healing, MIF also illustrates complex functions. MIF can captivate or drive away macrophages to the spot of wound based on the immediate

surroundings within the amniotic cavity. At the beginning of PPROM, MIF can prohibit macrophage migration, putting off the recovery response.[78] MIF might influence the inflammatory response stimulated by macrophages. Although few researches point out that it can boost an irritating state, obstructing tissue repair, others demonstrate inflammation reducing effect.[79,80] Additional researches are needed to find out the exact effect of MIF on inflammation in PPROM. MIF's outcome on tissue remodeling throughout PPROM recovery remains ambiguous. Moreover, there are certain studies suggesting that it could be a factor in collagen deposition, which is fundamental aspects of tissue repair.[81] However, further studies are required to completely perceive its influence on this process.

MIF's impact in the healing of PPROM seems to be complicated. Although it can initially prevent the mobilization of macrophages and potentially affect the inflammation, but its overall effects on tissue remodeling is still ambiguous. More research work is required to find out how MIF can be controlled to maximize the macrophage function and boost the successful healing after PPROM.

Connection between MIF and Macrophages in PPROM Healing:

It has been demonstrated that MIF can regulate macrophage functions, affecting their activation, recruitment, and polarization in different conditions that lead to inflammation.[82] Within the framework of PPROM, MIF might control the macrophage phenotype and role at the location of tear of the membrane, consequently influencing the inflammatory response & tissue repair process.[83] In response to this, macrophages can produce MIF, initiating a positive feedback loop maintaining inflammation and remodeling tissue.[84] There is a need for further research to clarify the precise mechanism that supports the connection between MIF and macrophages in PPROM healing and to explore the possible therapy methods that focuses on this pathway. Even though the exact process behind the connection between MIF and PPROM healing are still being figured out, existing evidences show that MIF can help in regulating inflammation, immune responses, tissue repair and angiogenesis, which are essential part of PPROM healing process.

Discussion

This review highlights the important role of immune regulation in the context of PPROM. Macrophages, as key immune cells, contribute to inflammatory phase and later stages of tissue repair. A balance action of M1 and M2 seems essential for proper repairing after membrane damage. The cytokine environment influences macrophage behavior, and among these signals, MIF emerges as a key regulator. Studies suggest that MIF may effect how efficiently macrophages clear damaged tissue and promote repair. However, the exact way MIF controls this switch between inflammation and healing remains unclear.

Most findings agree that excessive or prolonged inflammation, driven by cytokine like TNF and IL-1, can weaken membranes and delay healing. In contrast, a timely shift toward a healing response involving M2 macrophages could help restore tissue integrity. MIF might play role in controlling this shift, but further research is needed to define its specific actions.

Overall, the relationship between MIF and macrophages offers a promising area for further investigation. Understanding this connection could lead to new therapies aimed at improving recovery after PPROM and preventing side effects for both mother and baby.

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References

1. Gorczyca K, Kozioł MM, Kimber-Trojnar Ż, Kępa J, Satora M, Rekowska AK, et al. Premature rupture of membranes and changes in the vaginal microbiome—Probiotics. *Reprod Biol*. 2024;24(3):100899. https://doi.org/10.1016/j.repbio.2024.100899
2. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*. 2010;88(1):31–8. doi: 10.2471/BLT.08.062554
3. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. *Am J Obstet Gynecol*. 2011;205(3):191–8.
4. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75–84. https://doi.org/10.1016/S0140-6736(08)60074-4
5. Romero R, Quintero R, Oyarzun E, Wu YK, Sabo V, Mazor M, et al. Intraamniotic infection and the onset of labor in preterm premature rupture of the membranes. *Am J Obstet Gynecol*. 1988;159:661–6. https://doi.org/10.1016/S0002-9378(88)80030-9
6. McGregor JA, Lawellin D, Franco Buff A, Todd JK, Makowski EL. Protease production by microorganisms associated with reproductive tract infection. *Am J Obstet Gynecol*. 1986;154(1):109–14. https://doi.org/10.1016/0002-9378(86)90404-7

7. McGregor JA, French JI, Lawellin D, Franco Buff A, Smith C, Todd JK. Bacterial protease–induced reduction of chorioamniotic membrane strength and elasticity. *Obstet Gynecol*. 1987;69(2):167–74.
8. French JI, McGregor JA. The pathobiology of premature rupture of membranes. *Semin Perinatol*. 1996;20(5):344–68. https://doi.org/10.1016/S0146-0005(96)80002-4
9. Dennery PA. Effects of oxidative stress on embryonic development. *Birth Defects Res C Embryo Today*. 2007;81(3):155–62. https://doi.org/10.1002/bdrc.20098
10. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. *Reprod Biol Endocrinol*. 2005;3:28. https://doi.org/10.1186/1477-7827-3-28
11. Myatt L, Cui X. Oxidative stress in the placenta. *Histochem Cell Biol*. 2004;122(4):369–82. https://doi.org/10.1007/s00418-004-0677-x
12. Menon R. Oxidative stress damage as a detrimental factor in preterm birth pathology. *Front Immunol*. 2014;5:567. https://doi.org/10.3389/fimmu.2014.00567
13. Chai M, Barker G, Menon R, Lappas M. Increased oxidative stress in human fetal membranes overlying the cervix from term non labouring and post labour deliveries. *Placenta*. 2012;33(8):604–10. https://doi.org/10.1016/j.placenta.2012.04.014
14. Myatt L. Review: reactive oxygen and nitrogen species and functional adaptation of the placenta. *Placenta*. 2010;31(Suppl):S66–9. https://doi.org/10.1016/j.placenta.2009.12.021
15. Wisdom SJ, Wilson R, McKillop JH, Walker JJ. Antioxidant systems in normal pregnancy and in pregnancy induced hypertension. *Am J Obstet Gynecol*. 1991;165(6 Pt 1):1701–4. https://doi.org/10.1016/0002-9378(91)90018-M
16. Cindrova Davies T, Yung HW, Johns J, Jauniaux E. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. *Am J Pathol*. 2007;171(4):1168–79. https://doi.org/10.2353/ajpath.2007.070528
17. Coughlan MT, Permezel M, Georgiou HM, Rice GE. Repression of oxidant induced nuclear factor kappaB activity mediates placental cytokine responses in gestational diabetes. *J Clin Endocrinol Metab*. 2004;89(7):3585–94. https://doi.org/10.1210/jc.2003-031953
18. Bennett PR, Rose MP, Myatt L, Elder MG. Preterm labor: stimulation of arachidonic acid metabolism in human amnion cells by bacterial products. *Am J Obstet Gynecol*. 1987;156(3):649–55. https://doi.org/10.1016/0002-9378(87)90070-6
19. Ford-Hutchinson AW, Girard Y, Lord A, Jones TR, Cirino M, Evans JF, Gillard J, et al. The pharmacology of L 670,596, a potent and selective thromboxane/prostaglandin endoperoxide receptor antagonist. *Can J Physiol Pharmacol*. 1989;67(9):989–93. https://doi.org/10.1139/y89-155
20. Dietrich M, Block G, Norkus EP, Hudes M, Traber MG, Cross CE, Packer L. et al. Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma tocopherol in vivo after adjustment for dietary antioxidant intakes. *Am J Clin Nutr*. 2003;77(1):160–6. https://doi.org/10.1093/ajcn/77.1.160
21. Bauer ME, Jeckel CM, Luz C. The role of stress factors during aging of the immune system. *Ann N Y Acad Sci*. 2009;1153:139–52. https://doi.org/10.1111/j.1749-6632.2008.03966.x
22. Hass R, Sohn C. Increased oxidative stress in preeclamptic placenta is associated with altered proteasome activity and protein patterns. *Placenta*. 2003;24(10):979–84. https://doi.org/10.1016/S0143-4004(03)00174-7
23. Monboisse JC, Braquet P, Randoux A, Borel JP. Non enzymatic degradation of acid soluble calf skin collagen by superoxide ion: protective effect of flavonoids. *Biochem Pharmacol*. 1983;32(1):53–8. https://doi.org/10.1016/0006-2952(83)90651-2
24. Buhimschi IA, Buhimschi CS, Pupkin M, Weiner CP. Beneficial impact of term labor: nonenzymatic antioxidant reserve in the human fetus. *Am J Obstet Gynecol*. 2003;189(1):181–8. https://doi.org/10.1067/mob.2003.357
25. Lappas M, Permezel M, Rice GE. N-Acetyl cysteine inhibits phospholipid metabolism, proinflammatory cytokine release, protease activity, and nuclear factor kappaB DNA binding activity in human fetal membranes in vitro. *J Clin Endocrinol Metab*. 2003;88(4):1723–9. https://doi.org/10.1210/jc.2002-021677
26. Arechavaleta-Velasco F, Mayon-Gonzalez J, Gonzalez-Jimenez M, Hernandez-Guerrero C, Vadillo-Ortega F. Association of type II apoptosis and 92-kDa type IV collagenase expression in human amniochorion in prematurely ruptured membranes with tumor necrosis factor receptor-1 expression. *J Soc Gynecol Investig*. 2002;9(2):60–7. https://doi.org/10.1177/107155760200900203
27. Fortunato SJ, Menon R, Bryant C, Lombardi SJ. Programmed cell death (apoptosis) as a possible pathway to metalloproteinase activation and fetal membrane degradation in premature rupture of membranes. *Am J Obstet Gynecol*. 2000;182(6):1468–76. https://doi.org/10.1067/mob.2000.107330
28. Tanir HM, Sener T, Artan S, Kaytaz B, Sahin-Mutlu F, Ozen ME. Programmed cell death (apoptosis) in placentas from normal pregnancy and pregnancy complicated by term and preterm premature rupture of membranes. *Arch Gynecol Obstet*. 2005;273(2):98–103. https://doi.org/10.1007/s00404-005-0028-8
29. Menon R, Lombardi SJ, Fortunato SJ. TNF-alpha promotes caspase activation and apoptosis in human fetal membranes. *J Assist Reprod Genet*. 2002;19(4):201–4. https://doi.org/10.1023/A:1014898130008
30. Lonergan M, Aponso D, Marvin KW, et al. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), TRAIL receptors, and the soluble receptor osteoprotegerin in human gestational membranes and amniotic fluid during pregnancy and labor at term and preterm. *J Clin Endocrinol Metab*. 2003;88(8):3835–44. https://doi.org/10.1210/jc.2002-021905
31. George RB, Kalich J, Yonish B, Murtha AP. Apoptosis in the chorion of fetal membranes in preterm premature rupture of membranes. *Am J Perinatol*. 2008;25(1):29–32. https://doi.org/10.1055/s-2007-1004828
32. Menon R, Fortunato SJ. Fetal membrane inflammatory cytokines: a switching mechanism between the preterm premature rupture of the membranes and preterm labor pathways. *J Perinat Med*. 2004;32(5):391–9. https://doi.org/10.1515/JPM.2004.134
33. Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(3):467–78. https://doi.org/10.1016/j.bpobgyn.2007.01.008
34. Behnia F, Sheller S, Menon R. Mechanistic differences leading to infectious and sterile inflammation. *Am J Reprod Immunol*. 2016;75(4):505–16. https://doi.org/10.1111/aji.12496
35. Romero R, Miranda J, Chaemsaithong P, et al. Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med*. 2014;27(12):1228–36. https://doi.org/10.3109/14767058.2013.853320
36. Dayal S, Hong PL. Premature Rupture of Membranes. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532888/
37. Hay ED. Extracellular matrix. *J Cell Biol*. 1981;91(3 Pt 2):205s–23s. https://doi.org/10.1083/jcb.91.3.205s
38. Bourne GL, Lacy D. Ultra-structure of human amnion and its possible relation to the circulation of amniotic fluid. *Nature*. 1960;186:952–4. https://doi.org/10.1038/186952a0
39. Castillo-Castrejon M, Meraz-Cruz N, Gomez-Lopez N, Flores-Pliego A, et al. Choriodecidual cells from term human pregnancies show distinctive functional properties related to the induction of labor. *Am J Reprod Immunol*. 2014;71(1):86–93. https://doi.org/10.1111/aji.12179
40. King AE, Kelly RW, Sallenave JM, Bocking AD, Challis JR. Innate immune defences in the human uterus during pregnancy. *Placenta*. 2007;28(11–12):1099–106. https://doi.org/10.1016/j.placenta.2007.06.002

41. Vora S, Abbas A, Kim CJ, et al. Nuclear factor-kappa B localization and function within intrauterine tissues from term and preterm labor and cultured fetal membranes. *Reprod Biol Endocrinol*. 2010;8:8. https://doi.org/10.1186/1477-7827-8-8
42. Montenegro D, Romero R, Kim SS, et al. Expression patterns of microRNAs in the chorioamniotic membranes: a role for microRNAs in human pregnancy and parturition. *J Pathol*. 2009;217(1):113–21. https://doi.org/10.1002/path.2463
43. Bryant-Greenwood GD. The extracellular matrix of the human fetal membranes: structure and function. *Placenta*. 1998;19(1):1–11. https://doi.org/10.1016/S0143-4004(98)90092-3
44. Bryant-Greenwood GD, Yamamoto SY. Control of peripartal collagenolysis in the human chorion-decidua. *Am J Obstet Gynecol*. 1995;172(1 Pt 1):63–70. https://doi.org/10.1016/0002-9378(95)90085-3
45. Fortunato SJ, Menon R, Lombardi SJ. Collagenolytic enzymes (gelatinases) and their inhibitors in human amniochorionic membrane. *Am J Obstet Gynecol*. 1997;177(4):731–41. https://doi.org/10.1016/S0002-9378(97)70260-6
46. Vadillo-Ortega F, Gonzalez-Avila G, Furth EE, et al. 92-kd type IV collagenase (matrix metalloproteinase-9) activity in human amniochorion increases with labor. *Am J Pathol*. 1995;146(1):148–56.
47. Draper D, McGregor J, Hall J, Jones W, Beutz M, Heine RP, Porreco R. Elevated protease activities in human amnion and chorion correlate with preterm premature rupture of membranes. *Am J Obstet Gynecol*. 1995;173(5):1506-12. https://doi.org/10.1016/0002-9378(95)90640-1
48. Lei H, Vadillo-Ortega F, Paavola LG, Strauss JF 3rd. 92-kDa gelatinase (matrix metalloproteinase-9) is induced in rat amnion immediately prior to parturition. *Biol Reprod*. 1995;53(2):339-44. https://doi.org/10.1095/biolreprod53.2.339
49. Tsuruda T, Costello-Boerrigter LC, Burnett JC Jr. Matrix metalloproteinases: pathways of induction by bioactive molecules. *Heart Fail Rev*. 2004;9(1):53-61. https://doi.org/10.1023/B:HREV.0000011394.34355.bb
50. Vincenti MP, White LA, Schroen DJ, Benbow U, Brinckerhoff CE. Regulating expression of the gene for matrix metalloproteinase-1 (collagenase): mechanisms that control enzyme activity, transcription, and mRNA stability. *Crit Rev Eukaryot Gene Expr*. 1996;6(4):391-411. https://doi.org/10.1615/CritRevEukarGeneExpr.v6.i4.40
51. Vadillo-Ortega F, Estrada-Gutierrez G. Role of matrix metalloproteinases in preterm labour. *BJOG*. 2005;112(1):19-22. https://doi.org/10.1111/j.1471-0528.2005.00579.x
52. Park KH, Chaiworapongsa T, Kim YM, et al. Matrix metalloproteinase 3 in parturition, premature rupture of the membranes, and microbial invasion of the amniotic cavity. *J Perinat Med*. 2003;31(1):12-22. https://doi.org/10.1515/JPM.2003.002
53. Fortunato SJ, LaFleur B, Menon R. Collagenase-3 (MMP-13) in fetal membranes and amniotic fluid during pregnancy. *Am J Reprod Immunol*. 2003;49(2):120-5. https://doi.org/10.1034/j.1600-0897.2003.00012.x
54. Fortunato SJ, Menon R, Lombardi SJ. MMP/TIMP imbalance in amniotic fluid during PROM: an indirect support for endogenous pathway to membrane rupture. *J Perinat Med*. 1999;27(5):362-8. https://doi.org/10.1515/JPM.1999.049
55. Gomez R, Romero R, Edwin SS, David C. Pathogenesis of preterm labor and preterm premature rupture of membranes associated with intraamniotic infection. *Infect Dis Clin North Am*. 1997;11(1):135-76. https://doi.org/10.1016/S0891-5520(05)70347-0
56. Moore RM, Schatz F, Kumar D, Mercer BM, Abdelrahim A, Rangaswamy N, Bartel C, et al. Alpha-lipoic acid inhibits thrombin-induced fetal membrane weakening in vitro. *Placenta*. 2010;31(10):886-92. https://doi.org/10.1016/j.placenta.2010.07.012
57. Menon R, Fortunato SJ. The role of matrix degrading enzymes and apoptosis in rupture of membranes. *J Soc Gynecol Investig*. 2004;11(7):427-37. https://doi.org/10.1016/j.jsgi.2004.04.001
58. Sonnemann KJ, Bement WM. Wound repair: toward understanding and integration of single-cell and multicellular wound responses. *Annu Rev Cell Dev Biol*. 2011;27:237-63. https://doi.org/10.1146/annurev-cellbio-092910-154251
59. Cordeiro JV, Jacinto A. The role of transcription-independent damage signals in the initiation of epithelial wound healing. *Nat Rev Mol Cell Biol*. 2013;14:249-62. https://doi.org/10.1038/nrm3541
60. Landén NX, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci*. 2016;73(20):3861-85. https://doi.org/10.1007/s00018-016-2268-0
61. Reinke JM, Sorg H. Wound repair and regeneration. *Eur Surg Res*. 2012;49(1):35-43. https://doi.org/10.1159/000339613
62. Mogami H, Hari Kishore A, Akgul Y, Word RA. Healing of preterm ruptured fetal membranes. *Sci Rep*. 2017;7(1):13139. https://doi.org/10.1038/s41598-017-13296-1
63. Sopher D. The response of rat fetal membranes to injury. *Ann R Coll Surg Engl*. 1972;51(4):240-9.
64. Mogami H, Kishore AH, Word RA. Collagen type 1 accelerates healing of ruptured fetal membranes. *Sci Rep*. 2018;8(1):696. https://doi.org/10.1038/s41598-017-18787-9
65. Devlieger R, Gratacos E, Wu J, et al. An organ-culture for in vitro evaluation of fetal membrane healing capacity. *Eur J Obstet Gynecol Reprod Biol*. 2000;92(1):145-50. https://doi.org/10.1016/S0301-2115(00)00439-5
66. Abrahams VM, Morrison JC. Progesterone withdrawal and the initiation of human parturition: a review of the evidence. *BJOG*. 2008;115(2):220-33. https://doi.org/10.1111/j.1471-0528.2007.01634.x
67. Murray, P.J., Allen, J.E., Biswas, S.K., Fisher, E.A., Gilroy, D.W., Goerdt, S, et al. Macrophage activation and polarization: Nomenclature and experimental guidelines. *Immunity*. 2014;41(1):14-20. https://doi.org/10.1016/j.immuni.2014.06.008
68. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity*. 2010;32:593-604. https://doi.org/10.1016/j.immuni.2010.05.007
69. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol*. 2011;11:723-37. https://doi.org/10.1038/nri3073
70. Wang J, Xu H, Teng Y, et al. Macrophages in pregnancy complications. *J Reprod Immunol*. 2019;132:32-9. https://doi.org/10.1016/j.jri.2019.02.002
71. Stout RD, Jiang C, Matta B, et al. Macrophages secrete angiopoietin-like protein 2 during wound healing and fibrosis. *Am J Pathol*. 2009;176(1):344-55. https://doi.org/10.1016/j.ajpath.2008.11.077
72. Cunha TI, Silva TA, Peters DM, et al. Macrophages control fundamental processes in pregnancy. *Trends Immunol*. 2015;36(1):10-8. https://doi.org/10.1016/j.it.2014.10.004
73. Wynn TA, Chawla A, Pollard JW. Macrophage biology in diverse pathologic settings. *Annu Rev Pathol*. 2013;8:247-85. https://doi.org/10.1146/annurev-pathol-011111-140050
74. Mirza R, Delgado J, Elson CO, et al. Local delivery of FGF-2 promotes healing in a murine model of preterm premature rupture of membranes. *Am J Obstet Gynecol*. 2002;187(3):626-32. https://doi.org/10.1016/S0002-9378(02)01562-9
75. Sakai S, Iwamori M, Murayama T, et al. Macrophage migration inhibitory factor in parturition. *J Matern Fetal Neonatal Med*. 2007;20(11):1327-32. https://doi.org/10.1080/14767050701620223
76. Chaiworapongsa T, Romero R, Espinoza J, et al. Macrophage migration inhibitory factor in patients with preterm parturition and microbial invasion of the amniotic cavity. *J Matern Fetal Neonatal Med*. 2005;18(6):405-16. https://doi.org/10.1080/14767050500361703
77. Zhao Y, Shimizu T, Nishihira J, Koyama Y, Kushibiki T, Honda A, Watanabe H, et al. Tissue regeneration using macrophage migration inhibitory factor-impregnated gelatin microbeads in cutaneous wounds.

The American journal of pathology. 2005 Dec 1;167(6):1519-29. doi: 10.1016/S0002-9440(10)61238-2.
78. Krivokuća MJ, Vilotić A, Stefanoska I, Bojić-Trbojević Ž, Vićovac L. Macrophage migration inhibitory factor in human early pregnancy events and association with placental pathologies. Placenta. 2021;116:51–7. https://doi.org/10.1016/j.placenta.2021.02.007
79. Tilstam PV, Schulte W, Holowka T, Kim BS, Nouws J, Sauler M, et al. MIF but not MIF-2 recruits inflammatory macrophages in an experimental polymicrobial sepsis model. J Clin Invest. 2021;131(23): e127171 https://doi.org/10.1172/JCI127171
80. Trifone C, Salido J, Ruiz MJ, Leng L, Quiroga MF, Salomón H, et al. Interaction between macrophage migration inhibitory factor and CD74 in human immunodeficiency virus type I infected primary monocyte-derived macrophages triggers the production of proinflammatory mediators and enhances infection of unactivated CD4+ T cells. Front Immunol. 2018;9:1494. https://doi.org/10.3389/fimmu.2018.01494
81. Mitchell S, Logan A, Rao S. Macrophage migration inhibitory factor (MIF) regulates murine macrophage function in wound healing. *J Surg Res*. 2003;110(2):225-32.
82. Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. In: *Macrophages: Biology and Role in the Pathology of Diseases*. Springer; 2003. https://doi.org/10.1007/978-1-59259-309-5_6
83. Dudley DJ, Edwin SS, Mitchell MD, Branch DW. Induction of preterm birth in mice by RU486. Biol Reprod. 1997;56(1):66-9.
84. Díaz L, Noyola-Martínez N, Barrera D, Hernández G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-α-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol. 2012;95(1-2):65-72.