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Chorioamnionitis – A complex pathophysiologic syndrome

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ABSTRACT

Chorioamnionitis, inflammation of the amniochorionic membrane (fetal membranes) is a very common disease but a complex syndrome associated with pregnancy. It presents a clinical impasse due to lack of knowledge of specific etiologies associated with this condition making confident clinical interventions difficult. Recent reports provide insight into genetic, epigenetic, behavioral, psychosocial, molecular and pathophysiological factors that are associated with chorioamnionitis. However, a coordinated approach in understanding causality and lack of early indicators (clinical and biomarkers) has hampered gaining knowledge about the disease status preventing proper intervention. Several reviews have provided in-depth analysis of the histologic and clinical evidence associated with chorioamnionitis. In this review, we provide a novel perspective on chorioamnionitis based on recent evidences from scientific literature on inflammation, apoptosis and genetics.

1. Chorioamnionitis

'Chorioamnionitis' is defined as inflammation of the amniochorionic (fetal) membranes of the placenta in response to microbial invasion or due to other pathological process. It is prevalent in patients with preterm premature rupture of the membranes (pPROM) and spontaneous preterm birth (PTB, birth before 37 weeks gestation) [1–3]. The amniochorionic membranes form the outermost layer of the conceptus within the intrauterine cavity and consist of a contiguous layer of amniotic epithelial cells that overly chorionic cytotrophoblast cells imbedded in collagen-rich extracellular matrix. This unit acts as a barrier to protect the fetus from environmental agents (particularly microorganisms and sometimes toxins) that can complicate pregnancies. Chorioamnionitis, regardless of its infectious etiology, challenges the functional integrity of the membranes, making them vulnerable to other environmental insults with pathologic consequences during pregnancy. In most clinicopathologic reports, chorioamnionitis is characterized by neutrophil invasion into the fetal membranes, the initial and commonest inflammatory response to bacterial infection [4]. However, as we discuss below, the regulation of immune cell recruitment into inflamed tissues is specifically controlled by selective chemokines, and we will consider the potential significance of macrophages, T cells and other immunocytes as possible mediators of chorioamnionitis.

Chorioamnionitis is traditionally defined under two main classifications: **histologic** – based on microscopic evidence of inflammation of the membranes (as noted above, infiltration of polymorphonuclear leukocytes and other immunocytes, such as macrophages and T cells) [4–10] and **clinical** – based on clinical manifestations of local and systemic inflammation (fever >37.5 °C), uterine tenderness, abdominal pain, foul smelling vaginal discharge, maternal [>100 beats/min] and fetal tachycardia [>160 beats/min] and elevated white blood cell count (>15,000 cells/mm^3) [11–15]. More recently the clinical category has been supported by changes in inflammatory biomarker profiles [16–18] (discussed in detail below). Regardless of these standard definitions, understanding chorioamnionitis is challenging as it reflects a heterogeneous group of risk factors, pathways and presentations. Throughout the literature significant ambiguity exists in case definitions and interpretation of histologic evidence, creating difficulty in understanding the prevention of chorioamnionitis [19]. As a result, neither a definitive screening strategy nor specific clinical interventions are available, and preterm birth and pPROM associated with chorioamnionitis remain major threats to pregnancy.

This review is intended to provide an overview and synthesis of a vast amount of existing literature on chorioamnionitis and to emphasize emerging pathophysiologic pathways and areas of

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future research. Although chorioamnionitis often occurs in conjunction with inflammation of other gestational tissues, such as decidua (deciduitis), placental villi (villitis), and the umbilical cord (funisitis), our discussion will be limited to the amniochorionic membranes.

2. Infectious etiology of chorioamnionitis, an historical prospective

In 1970s, MacVicar was among the first to speculate that clinical and histologic chorioamnionitis are either a cause or consequence of microbial invasion of the amniotic cavity or intraamniotic infection (IAI), i.e., the presence of microbes in the AF [20]. However, even earlier studies supported a strong association between infection and chorioamnionitis. Kobak identified bacteremia as a cause of IAI and placentitis [21] that was later confirmed by Knox and Hoerner [22], who reported histologic signs of infection and inflammation adjacent to the site of membrane rupture. In 1966, Hawkinson and Schulman found lower genital tract infection (cervicitis and vaginitis) was more common in women with pPROM and its control could potentially decrease pPROM and preterm labor [23]. Gravett's study in 1986 supported Schulman's findings demonstrating that the presence of bacterial vaginosis was significantly associated with pPROM when compared to a group with no bacterial vaginosis [24]. Reviews by Romero [25–27] and Gibbs [28] documented that commensal vaginal microbes, agents of asymptomatic and symptomatic bacteriuria, also can ascend into the intrauterine cavity, breach the fetal membranes and establish IAI.

Animal model studies in mice and rabbits showed that administration of bacterial endotoxin could lead to abortions [29,30]. Later several other scientists reported an association between systemic maternal infections and preterm birth [25,31]. Similarly IAIs were reported in >70% of pPROM, and the latter complicate one third of preterm births [28].

3. Incidence of histologic chorioamnionitis

Histologic chorioamnionitis has been associated with IAI and bacteria can be cultured from the amniotic fluid (AF) in 72% of cases of PTB [31]. Although not proven, it is speculated that chorioamnionitis is associated with low birth weight (LBW <2500 g) in preterm infants, suggesting that a fetal stress response to chronic infection leads to LBW [32]. Findings by other scientists also indicate that women with reduced AF volume and pPROM had a higher risk of infection and a greater chance of PTB associated with histologic chorioamnionitis [28,29]. Placental examination [33] found that only 33% of preterm laboring women with intact membranes had histologic chorioamnionitis whereas its rate was 80% in women with pPROM and PTB [4]. It should be noted that older studies without uniform definitions of histologic chorioamnionitis have contributed to inconsistencies in the literature.

4. Bacterial infections and initiation of inflammation

Based on the findings described above, chorioamnionitis can be considered as a surrogate measure of IAI. Anaerobic, aerobic and atypical bacteria contribute to the list of microbes associated with chorioamnionitis. Several reports and reviews have documented the microbiology and microbial pathogenesis in chorioamnionitis, pPROM and preterm birth and the readers are encouraged to review those references for details [3]. Bacterial species identified in intraamniotic biofilms, AF sludge with sonographic evidence of aggregates of dense particulate matter close to the internal cervical os, have been associated with chorioamnionitis, pPROM and preterm birth in asymptomatic subjects [34–39]. Romero et al. have reported that subjects with AF sludge had a significantly higher frequency of IAI, clinical and histologic chorioamnionitis than patients without sludge [40–43]. Curiously, AF cultures may yield negative results or distinctly different bacterial species than those isolated from sludge. Activation of inflammatory pathways resulting in pPROM and preterm birth by microbes in the sludge vs. microbes cultivated from AF also can be different and hence complicate the clinical picture. The finding of microbes in women with clinical and histologic chorioamnionitis and preterm labor resistant to tocolysis is a good indicator that the presence of bacteria, multitudes of antigens, and their metabolites in the amniotic cavity can be the primary initiators of preterm labor pathways [44–47]. In vitro studies have documented initiation of host inflammatory responses by bacterial products such as phospholipase A2, endotoxin, peptidoglycan polysaccharide, and proteolytic enzymes. Research done during 1990s clearly established the importance of a host inflammation response in pPROM and preterm birth, in addition to the mere presence of bacteria and their products. It is has been argued that the critical concentration or numeric quantity of microbes or antigens sufficient to induce pPROM or PTB is never achieved in the intrauterine compartments [48–52]. Secondly, microbial enzymes are not sufficient to cause matrix degradation associated with chorioamnionitis and pPROM [53–55]. Therefore host inflammatory responses are conjectured to be the primary effectors of the events resulting in pPROM and preterm birth. Multiple reviews have substantiated the contributory role of inflammatory processes as responses to infection [53–62]. Unfortunately, homogeneity cannot be expected in disease progression or pregnancy outcome depending on: 1) type and titer of microorganisms; 2) their localization within the intrauterine cavity; 3) antigencity (capacity to induce immune response); 4) inflammatory response elicited; and 5) initiators of a pathophysiologic pathways and uterotonic effectors that culminate in labor in cases with pPROM and PTB.

5. Inflammatory biomarkers as indicators of chorioamnionitis

IAI initiates a cascade of inflammatory processes that recruit immunocytes into the uterine cavity. Different classes of chemokines, chemoattractant proteins for immune cells, display considerable specificity. For example, whereas interleukin (IL)-8 and ENA-78 and potent attractants for neutrophils, monocyte chemotactic protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), and RANTES predominantly recruit monocytes and dendritic cells, while lymphotactin and IP-10 stimulate T cell migration and T cell mediated mast cell activation. We and others have studied chemokines extensively in the nonpregnant endometrium [63] and in preeclampsia [64]. Immunocyte infiltration is evident in the histologic evaluation of the affected amniochorion membranes, with the accumulation of neutrophils representing the first line of defense. Macrophage, T cell and dendritic cell invasion, along with the presence of microbes support this pathogenic process. Decidua, the maternal tissue adherent to amniochorion, also is infiltrated by macrophages [56]. Pathological evaluation of chorioamnionitis should include all immunocytes and not to be limited to neutrophils. Although over 70% of cases with histologic chorioamnionitis have documented IAI, it is important to note that some cases with histologic inflammation can be due to a variety of noninfectious causes, including fetal hypoxia, amniotic fluid pH changes, meconium and other nonspecific responses [9].

Moreover, lack of histologic or microbiological evidence does not rule out an underlying inflammatory process as subclinical infections may not uniformly yield these classic findings. Since histologic evaluation of the membranes is impossible prior to delivery,