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The role of inflammation and infection in preterm birth

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Abstract

Inflammation has been implicated in the mechanisms responsible for preterm and term parturition, as well as fetal injury. Out of all of the suspected causes of preterm labor and delivery, infection and/or inflammation is the only pathological process for which both a firm causal link with preterm birth has been established and a molecular pathophysiology defined. Inflammation has also been implicated in the mechanism of spontaneous parturition at term. Most cases of histopathological inflammation and histological chorioamnionitis, both in preterm and term labor, are sub-clinical in nature. The isolation of bacteria in the amniotic fluid, known as microbial invasion of the amniotic cavity, is a pathological finding; the frequency of which is dependent upon the clinical presentation and gestational age. This article reviews the role of inflammation in preterm and term parturition.

Keywords

preterm labor; cytokines; fetal inflammatory response syndrome; chemokines; microbial invasion of the amniotic cavity

Introduction

Inflammation has been implicated in the mechanisms responsible for term and preterm parturition as well as fetal injury.[1–10] Of all suspected causes of preterm labor and delivery, infection and/or inflammation is the only pathologic process for which both a firm causal link with preterm birth has been established and a molecular pathophysiology defined.[11] Inflammation has also been implicated in the mechanism of spontaneous parturition at term. This article will review the role of inflammation in preterm and term parturition.

The spectrum of inflammation: clinical, histopathological and molecular

Inflammation is the basic process by which tissues of the body respond to insults.[12] The first comprehensive description of the clinical signs of inflammation has been attributed to Celsus,[13] who introduced four of the five classical signs (*calor, dolor, rubor, and tumor),*

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which translate to heat, pain, redness, and swelling. Galen added the fifth sign (*function laesa),* which means impaired function.[13] Since that time, clinical inflammation has been classically defined by the presence of these five cardinal signs, all of which reflect the effects of chemokines, cytokines and other inflammatory mediators on local blood vessels and tissues.[14,15] Vasodilatation and increased permeability account for the changes in temperature, redness and swelling (to some extent), while the migration of cells into tissue and the action of their mediators on the nerve endings account for pain and swelling.[15] In contrast, histologic inflammation is defined by the infiltration of tissue by neutrophils, macrophages, and lymphocytes.[13] The type of cell infiltrate is used to classify inflammation into acute or chronic. However, this classification may have some limitations in reproductive tissues in which there is physiologic infiltration of inflammatory cells. For example, neutrophils are normally present in menstrual endometrium,[16] and the differential diagnosis between acute endometritis and perimenstrual endometrium requires examination of the magnitude of the infiltration.[17] Pathologic examination has been the gold standard for the diagnosis of inflammation. However, chemotactic signals must be present for the white blood cells to migrate to the site of injury or infection. Thus, there is a window of time in which a "molecular signature of inflammation", is present before histologic evidence is observed. For example, analysis of the transcriptome (see below)[18] or the detection of inflammatory markers in body fluids (e.g. plasma, cerebrospinal fluid or amniotic fluid) may allow detection of early signs of inflammation that may not be detectable by conventional pathology.

A clear understanding of the spectrum of inflammation is important because there is a common misconception that the absence of systemic clinical signs, such as fever, chills, leucocytosis, etc., makes inflammation (and sometimes infection) unlikely. In reality, the evidence, as well as the understanding of pathophysiology, suggests that the opposite is the case. Most cases of histopathological inflammation are subclinical in nature. This is also the case in histologic chorioamnionitis, both at term (B.H. Yoon, R. Romero, et al., unpublished observations) and preterm delivery.[19,20]

Inflammation: from pathology to physiology and back

Inflammation is widely regarded as the fundamental mechanism of multicellular organisms to deal with insults, both of infectious and non-infectious nature. Inasmuch as the primary force shaping the evolution of the immune system is defense against microorganisms, it is not surprising that the mechanisms of inflammation were discovered when studying infectious diseases.[21] However, inflammation also plays a central role in physiologic processes, particularly in the reproductive tract. The rupture of an ovarian follicle,[22] the implantation of the blastocyst,[23,24] menstruation,[25] and parturition[26,27] are characterized by cellular and molecular events which are found in pathologic inflammation (i.e. those associated with disease).

The value of inflammation

In the presence of invading microorganisms, inflammation accomplishes three main goals: (1) to deliver cells and molecules to suppress the infection; (2) to generate a physical barrier to the spread of the infection; and (3) to promote repair of the injured tissue.[15]

Cells called to the site of injury include macrophages, neutrophils, and lymphocytes. Molecules released during the course of inflammation include antimicrobial peptides, cytokines, chemokines, and other inflammatory mediators such as prostaglandins, leukotrienes, complement, etc.[15] Some of these molecules change the state of activation of macrophages and neutrophils so that microbial killing is enhanced (i.e. through the release of reactive oxygen species). For example, activation of NADPH oxydase converts molecular oxygen into superoxide, which in turn is transformed by superoxide dismutase into hydrogen peroxide. This molecule has antimicrobial properties and can be transformed by peroxidase to hypochlorite and hydroxyl radicals. Superoxide, hydrogen peroxide, and hydroxyl radicals are called reactive oxygen species or reactive oxygen metabolites, and are important in microbial killing.[15] When these molecules are released outside of phagocytes, they can injure other host cells. The state in which there is an excess generation and activity of reactive oxygen metabolites is called oxidative stress and is a mechanism of disease in systemic inflammation (e.g. sepsis,[28] and preeclampsia[29–32]).

A second major goal of inflammation is to prevent the spread of microorganisms, and this is often accomplished by activation of the coagulation system and formation of thrombi in blood vessels draining the infected/inflamed sites. Thrombin, the rate limiting step of coagulation, has also pro-inflammatory properties. Indeed, in vitro experiments had demonstrated that thrombin enhances the LPS-induced interleukin (IL)-1 and tumor necrosis factor-α (TNF-α) in monocytes.[33]

Inflammation as a response to “danger signals” (microbial or nonmicrobial)

Injury can be the result of exposure to microorganisms or non-microbial-related insults. The consequences of microbial invasion and proliferation are well known and, therefore, will not be discussed in this section. However, the means by which non-microbial insults can injure and be recognized by the host are less well known. For example, exposure to an allergen or a transplanted organ can cause disease because the immune system recognizes the allergen or the organ as non-self. How is this accomplished? The immune system has evolved to identify the non-self using pattern recognition receptors (PRR) which are receptors that can identify repeating patterns of molecular structure, common to most microorganisms.[15] However, it is now realized that these pattern recognition receptors can be used not only to sense the presence of microorganisms but also to identify “danger signals”.[34] The basic premise of the “danger model” is that the immune system is more concerned with damage than with foreignness (“non-self”), and that an immune reaction is set into action because of “alarm signals” from injured tissues rather than by the recognition of non-self.[34]

Examples of “alarm signals” are those released by necrotic cells of the host that have been injured by microbial or non-microbial insults. The first pattern recognition receptors identified were Toll-like receptors[35,36] and the ligands for these receptors were originally thought to be of microbial origin (e.g. endotoxin, peptidoglicans, viral RNA, etc.).[15,35,36] It is now known that Toll-like receptors can recognize not only microbial products but also host signals produced in the context of injury, such as heat-shock proteins.[37] Thus, the “danger model” of immunity provides a framework to understand the nature of the immune

response and it releases it from the previously held paradigm, which was dependent largely on the self versus non-self concept.[34]

The immune response has two components: the innate and the adaptive. The innate mechanisms acts immediately, are non-specific, and lack immunological memory. The adaptive immune response, on the other hand, is specific, takes time to develop, and has memory.[15] Inflammation is part of the innate immune response. However, it is now known that innate immunity orchestrates an appropriate adaptive immune response, and inflammation would also be part of the adaptive response.[15] In conclusion, inflammation can be thought as central to maintaining tissue homeostasis. Exaggerated or prolonged inflammation or lack of an adequate inflammatory response can lead to disease.

Infection as a cause of premature labor

Evidence of causality: Infection is a frequent and important mechanism of disease in premature labor and delivery.[5,8,38,39] The evidence in support of this includes: 1) intrauterine infection or systemic administration of microbial products to pregnant animals can result in preterm labor and delivery;[8,40–52] 2) extra-uterine maternal infections such as malaria,[53–58] pyelonephritis,[59–63] pneumonia,[64] and periodontal disease have been associated with premature parturition;[65–68] 3) subclinical intrauterine infections are associated with preterm labor and delivery;[69] 4) patients with intra-amniotic infection[70–72] or intra-uterine inflammation (defined as an elevation of amniotic fluid concentrations of cytokines[73,74] and matrix degrading enzymes[75]) in the midtrimester are at risk for subsequent preterm delivery; 5) antibiotic treatment of ascending intrauterine infections can prevent prematurity in experimental models of chorioamnionitis;[49,76] and 5) treatment of asymptomatic bacteriuria prevents prematurity.[77,78]

The frequency and clinical significance of intrauterine infection: Intrauterine infections caused by bacteria are considered to be the leading cause of infection-associated preterm birth. The amniotic cavity is considered to be sterile as less than 1% of women not in labor at term will have bacteria in the amniotic fluid. Therefore, the isolation of bacteria in the amniotic fluid is a pathologic finding, which we have defined as microbial invasion of the amniotic cavity, or MIAC. Most of these infections are subclinical in nature and cannot be detected without amniotic fluid analysis. The frequency of MIAC depends upon the clinical presentation and gestational age. In patients with preterm labor with intact membranes, the rate of positive amniotic fluid cultures is 12.8%.[39] However, among those patients who have preterm labor with intact membranes and deliver a preterm neonate, the frequency is 22 %. Among women with preterm PROM, the rate of positive amniotic fluid cultures at admission is 32.4%,[39] however, at the time of the onset of labor, as many as 75% of patients will have MIAC,[79] suggesting that microbial invasion occurs during the latency period.

The frequency of MIAC among women with cervical insufficiency is up to 51%.[80,81] If the cervix is short (as determined by sonographic cervical length of less than 25 mm) MIAC occurs in 9% of cases.[82] Finally, the frequency of MIAC in twin gestations is 11.9%.[83,84] Of

interest, in twin gestations in whom MIAC is detected, the presenting sac is nearly always involved, while the other amniotic cavity may not have MIAC.[84]

Patients with MIAC are more likely to deliver preterm, have spontaneous rupture of the membranes, develop clinical chorioamnionitis, and experience adverse perinatal outcome than patients with preterm labor or preterm PROM with sterile amniotic fluid.

An interesting and consistent observation is that the lower the gestational age at presentation (preterm labor with intact membranes or preterm PROM), the higher the frequency of positive amniotic fluid cultures.[85,86] Thus, infection is more prevalent in the earlier spontaneous preterm birth.

Microbiology of intrauterine infection: The most common microorganisms found in the amniotic cavity are genital Mycoplasmas and, in particular, *Ureaplasma urealyticum*.[38,87] However, other microorganisms found in the amniotic cavity include *Mycoplasma hominis*, *Streptococcus agalactiae, E. coli, Fusobacterium* species, and *Gardnerella vaginalis*.[38,87] Of interest, with the use of molecular microbiologic techniques, organisms normally found in the oral cavity have been detected in amniotic fluid of women with preterm labor.[88] This observation raises questions as to the pathway used by these organisms to reach the amniotic cavity (see below).

Significance of MIAC detected only by molecular microbiology techniques: The prevalence of MIAC is based on the results of standard microbiologic methods (i.e. cultivation techniques). A positive culture can only be obtained if the culture conditions in the laboratory are able to support the growth of a particular microorganism. Inasmuch as the growth requirements of all microorganisms are unknown, a negative culture cannot be taken to exclude definitively the presence of a microorganism. In other words, while a positive culture is indicative of MIAC, a negative culture indicates that the laboratory was not able to grow bacteria from the specimen, either because bacteria was absent (a true negative result) or because the laboratory conditions did not support the growth of a specific microorganism (a false negative result). It is noteworthy that only 1% of the whole microbial world can be detected by cultivation techniques ("the great plate count anomaly").[89–91] Consequently, the frequency of MIAC reported herein represents minimum estimates. These figures are likely to change with the introduction of more sensitive methods for microbial recovery and identification. Indeed, several investigators have demonstrated that the prevalence of MIAC is higher when molecular microbiologic techniques are used to detect conserved sequences in prokaryotes (e.g. bacterial 16S rDNA with PCR).[92–95]

The clinical significance of MIAC detected purely by molecular microbiology techniques, but which cannot be detected by cultivation techniques, has been recently addressed. Patients with a positive PCR for *Ureaplasma urealyticum* but negative culture have similar adverse outcomes than patients with a positive amniotic fluid culture for this microorganism and worse outcomes than patients with sterile amniotic fluid and negative PCR.[96,97] Moreover, patients with a positive PCR but a negative culture have the same degree of inflammation (amniotic fluid IL-6, histologic chorioamnionitis or funisitis) as those with a positive

amniotic fluid culture.[97] Collectively, this evidence suggests that the presence of microbial footprints detected by PCR is associated with adverse outcome.

Intrauterine infection can also be present in the absence of a positive amniotic fluid culture for microorganisms, or a negative PCR. Specifically, if the infection is localized to the decidua or the space between amnion and chorion, microorganisms may not be detected in the amniotic cavity.[86] There is evidence that the rate of microbial colonization in the chorioamniotic space is higher than that observed in the amniotic cavity.[86] Patients with positive amniotic fluid cultures in the membranes, but negative cultures in the amniotic fluid, often have elevation of amniotic fluid concentrations of indicators of inflammation, such as IL-6.[86] Therefore, some patients with intra-amniotic inflammation but negative cultures in the amniotic fluid may have intra-uterine infection in the extra-amniotic space.

Microorganisms in the chorioamniotic membranes – is it always indicative of pathology?—The amniotic cavity is normally considered sterile for bacteria, even with the use of molecular microbiologic techniques. In contrast, fluorescent *in situ* hybridization with a DNA probe specific for conserved regions of bacterial DNA (the 16S ribosomal RNA) has detected bacteria in the fetal membranes of up to 70% of women undergoing elective cesarean section at term.[98] Bacteria are often present in the membranes of patients with preterm labor and intact membranes, and patients with preterm PROM.[98] These findings suggest that the presence of bacteria alone is not sufficient to cause preterm labor and delivery, and that microbial colonization of the chorioamniotic membranes may not always elicit a fetal or maternal inflammatory response. However, preterm labor is more frequent when a fetal inflammatory response in elicited as diagnosed by an increase in IL-1 and IL-6 and a decrease in IL-10.[98]

MIAC as a chronic process: Although chorioamnionitis is traditionally considered an acute process, evidence that MIAC exists for an extended period of time is mounting. Cassell et al.[70] were the first to report the recovery of genital Mycoplasmas from 6.6% (4/61) of amniotic fluid samples collected by amniocentesis between 16 and 21 weeks of gestation. Two women had positive cultures for *Mycoplasma hominis* and two for *Ureaplasma urealyticum*. Women with *M. hominis* delivered at 34 and 40 weeks without neonatal complications, while those with *U. urealyticum* had premature delivery, neonatal sepsis and neonatal death at 24 and 29 weeks. Subsequently, Gray et al.[71] reported a 0.37% prevalence (9/2461) of positive cultures for *U. urealyticum* in amniotic fluid samples obtained during second trimester genetic amniocentesis. After exclusion of a therapeutic abortion case, all women (8/8) with positive amniotic fluid cultures had either a fetal loss within four weeks of amniocentesis (n=6) or preterm delivery (n=2). All had histological evidence of chorioamnionitis. These observations suggest that microbial invasion could be clinically silent in the midtrimester of pregnancy and that pregnancy loss/preterm delivery could take weeks to occur. A similar finding was reported by Horowitz et al.,[72] who detected *U. urealyticum* in 2.8% (6/214) of amniotic fluid samples obtained between 16 and 20 weeks of gestation. The rate of adverse pregnancy outcome (fetal loss, preterm delivery and low birthweight) was significantly higher in women with a positive amniotic fluid culture than in those with a negative culture (3/6 [50%] versus 15/123 [12%]; P=0.035).

Pathways of intra-amniotic infection: Microorganisms may gain access to the amniotic cavity and fetus using any of the following pathways: (1) ascending from the vagina and the cervix; (2) hematogenous dissemination through the placenta (transplacental infection); (3) retrograde seeding from the peritoneal cavity through the fallopian tubes; and (4) accidental introduction at the time of invasive procedures such as amniocentesis, percutaneous fetal blood sampling, chrorionic villous sampling, or shunting.[7] The most common pathway of intrauterine infection is the ascending route (Figure 1).

Accumulating evidence supports a relationship between periodontal disease and premature labor and delivery.[66,68,99–103] The mechanism underlying this association has not been definitively established, however, there is experimental evidence that microorganisms found in the gingival crevice can be isolated from the amniotic fluid, suggesting that maternal bacteremia and transplacental passage could account for some of these infections. Indeed, a humoral fetal response has been demonstrated by Boggess et al.[104]

Microbial products in the amniotic cavity: The adverse events associated with microbial invasion can be due to the proliferation of intact microorganisms or bacterial products. For example, the cell wall of Gram-negative bacteria contains lipopolysaccharide (LPS) or endotoxin. This potent agent is capable of inducing endotoxic shock and death.[105] Gram-positive bacteria lack LPS but contain peptidoglycans (PGN) and lipoteichoic acid, essential components of the bacterial wall.[106] Mycoplasmas have products such as lipoglycans.[107] Many of the effects of microorganisms are mediated by these products, which can be released during bacterial death. Consequently, even nonviable bacteria may exert deleterious effects. LPS, peptidoglycans and lipoglycans are recognized by Toll-like receptors and other pattern recognition molecules and can elicit an inflammatory response.

Bacterial endotoxin in amniotic fluid was first identified in 1987.[108] Subsequently, it was found that the concentrations of these microbial products were significantly higher in women with preterm labor than in those with microbial invasion without preterm labor.[109] There is a paucity of data about the amniotic fluid concentration of other microbial products. A number of experimental studies have determined that endotoxin administration into the amniotic cavity[110,111] or intraperitoneally[48,112,113] can result in an inflammatory response and potent biological effects in the fetal lung.[114–116] Moreover, intrauterine bacterial inoculation, in an ascending model of intra-amniotic infection, was associated with histologic evidence of brain white matter damage.[117]

Detection of viral genome in the amniotic fluid and adverse pregnancy outcome: A viral genome is detected in the amniotic fluid of up to 15% of asymptomatic low-risk pregnancies[118–121] and 41% of pregnancies at risk for viral infection.[122–124] The most common viral DNA isolates, either in low- or high-risk pregnancies, are adenovirus, cytomegalovirus (CMV) and enterovirus.[119–124]

Burguete et al[125] performed a multicenter study to determine the prevalence of adeno-associated parvovirus (AAV) in midtrimester amniotic fluid samples, using PCR specific for DNA sequences of AAV. The prevalence of amniotic fluid positive for AAV by PCR was 27% (64/238). Moreover, patients with amniotic fluid positive for AAV by PCR had a higher

frequency of preterm labor and preterm PROM than those with AF negative for AAV by PCR.[125] Reddy et al.[124] found an association between detection of a viral genome in the amniotic fluid and adverse pregnancy outcome. PCR was conducted for CMV, parvovirus B19, adenovirus, enterovirus, HSV, EBV, and RSV in 147 pregnancies. One hundred and thirty-eight fetuses were chromosomally normal, and among these, 25 (18%) had a positive amniotic fluid by PCR. These fetuses were more likely to deliver prematurely, have preterm PROM, non-immune hydrops, low birth weight or an intrauterine fetal demise. When only structurally normal fetuses were analyzed, those with a positive amniotic fluid for viral genome by PCR were more likely to die *in utero* and have both a lower gestational age and lower birth weight at delivery.

Inflammation as a mechanism for preterm parturition

An overview of the inflammatory response: The first line of defense against infection is provided by the innate immune system. Epithelial surfaces (skin and mucous membranes) represent the first physical barrier between the body and microorganisms. Injuries to the epithelial surface provide a logical point of entry of microorganisms. These injuries can result from accidents or physiologic processes (e.g. menstruation). Thus, a sexually transmitted microorganism may cause infection if it gains access to the endometrial wound during menstruation. However, bacteria can cross intact epithelial barriers. There is experimental[126] and clinical evidence[38,108] that bacteria can cross intact chorioamniotic membranes. Epithelium, however, represents more than a physical barrier against microorganisms. Most epithelia produce natural anti-microbial peptides (e.g. alpha-defensins and beta-defensins),[127] which can kill bacteria by damaging their cell membranes.[128–131] For example, the fetal lung produces surfactant proteins (SP-A[132,133] and SP-D[133]), that belong to the collectin family, which can bind microorganisms and facilitate phagocytosis (opsonization). Moreover, SP-A and SP-D have been shown to be involved in clearance of bacteria, fungi, and apoptotic and necrotic cells, down-regulation of allergic reaction, and resolution of inflammation.[134]

Another mechanism of host defense against infection derives from the metabolic products of bacteria. For example, lactobacilli, which colonize the vagina shortly after birth, produce lactic acid and lower the pH of the vagina. This unique partnership between vaginal tissues and species-specific strains of lactobacilli has been considered responsible for enabling internal fertilization in the evolution of mammals from amphibians.[135] In addition to the low pH, some strains of lactobacilli also produce antimicrobial products (bacteriocin-like compounds) which prevent the growth of pathogenic bacteria.[136,137]

The innate component of the immune system also provides immediate protection from microbial challenge by recognizing the presence of micro-organisms, thus preventing tissue invasion and/or eliciting a host response to limit microbial proliferation (inflammation).[15] One of the mechanisms by which the innate immunity recognizes micro-organisms is by using pattern recognition receptors (PRRs) which bind to repeating patterns of molecular structures present in the surfaces of microorganisms.[15] PRRs are classified based on their function and subcellular localization into the following groups: (1) soluble PRRs such as “the acute phase proteins” Mannan Binding Lectin (MBL) and C-Reactive Protein (CRP),

which act as opsonins to neutralize and clear pathogens through the complement and phagocytic systems; (2) transmembrane PRRs, which include scavenger receptors, C-type lectins and the Toll-like receptors (TLRs); (3) intracellular PRRs, including Nod1 and Nod2, RIG-1 and MDA-5, which mediate recognition of intracellular pathogens (e.g. viruses).[138]

Ten different TLRs have been recognized in humans.[15] TLR-4 recognizes the presence of LPS (Gram-negative bacteria), and TLR-2 recognizes peptidoglycans, lipoproteins, and zymosan (Gram-positive bacteria, mycoplasmas, and fungi). TLR-3 recognizes double-stranded RNA (viruses). The ligand for TLR-5 is flagellin.[15,139,140]

Ligation of TLRs results in activation of NFκB, which, in turn, leads to the production of cytokines, chemokines, and anti-microbial peptides.[15] Moreover, activation of the Toll pathway also induces surface expression of co-stimulatory molecules required for the induction of adaptive immune responses such as CD-80 and CD-86. These molecules, in combination with antigenic microbial peptides, presented by MHC class II proteins in dendritic cells and macrophages can activate naïve CD4 T-cells which, in turn, initiate most adaptive immune responses.[15]

The genital tract and trophoblasts have innate immune receptors: Toll-like receptors (TLR)-1, −2, −3, −5, and −6, have been identified in the epithelia from the vagina, ecto- and endocervix, endometrium, and uterine tubes.[141] Of note, TLR-4 has only been demonstrated in the endocervix, endometrium, and uterine tubes, but not in the vagina and ectocervix.[141] This has been interpreted as evidence that TLR-4 may participate in the modulation of immunological tolerance in the lower parts of the female reproductive tract and in host defense against infection.[141] Similarly, trophoblast cells are able to recognize and respond to pathogens through the expression of Toll-like receptors. We have demonstrated that trophoblast cells are able to recognize pathogens through the expression of TLR-2 and TLR-4. However, activation of different TLRs appears to generate distinct trophoblast cell responses. Indeed, in vitro studies have demonstrated that TLR-4 ligation by microbial products (LPS) promotes cytokine production, while ligation of TLR-2 to peptidoglycan and lipoteichoic acid induces apoptosis in first trimester trophoblast cells.[142] These findings suggest that a pathogen, through TLR-2, may directly promote trophoblast cell death[142] observed in a number of pregnancy complications including spontaneous abortion,[143] intrauterine growth restriction[144,145] and preeclampsia.[144,146]

The importance of TLRs in preterm parturition: Since TLRs are crucial for the recognition of microorganisms, it will be anticipated that defective signaling through this pattern recognition receptor will impair bacteria-induced preterm labor. This is indeed the case. A strain of mice which has a spontaneous mutation for TLR-4 is less likely than wild type mice to deliver preterm after intrauterine inoculation of heat killed bacteria or LPS.[110,147] In pregnant women, TLR-2 and TLR-4 are expressed in the amniotic epithelium.[148] Moreover, spontaneous labor at term and preterm delivery with histologic chorioamnionitis, regardless of the membrane status (intact or ruptured), are associated with an increased mRNA expression of TLR-2 and TLR-4 in the chorioamniotic membranes.[148] These observations suggest that the innate immune system plays a role in parturition, whether or not there is demonstrable intra-amniotic infection/inflammation.

The role of pro-inflammatory cytokines (IL-1 and TNF-α): A solid body of evidence indicates that cytokines play a central role in the mechanisms of inflammation/infection-induced preterm parturition.[2,26,69,149–159] IL-1 was the first cytokine to be implicated in the onset of preterm labor associated with infection.[149] Evidence in support of participation of IL-1 included that: (1) IL-1 is produced by human decidua in response to bacterial products;[160] (2) IL-1 can stimulate prostaglandin production by human amnion and decidua;[161] (3) IL-1 concentration and bioactivity was increased in the amniotic fluid of women with preterm labor and infection;[162] (4) IL-1 could stimulate myometrial contractions[163] (Bulletti C, personal communication, 2002); and (5) administration of IL-1 to pregnant animals induced preterm labor and delivery,[164] a phenomenon that could be blocked by the administration of its natural antagonist, IL-1 receptor antagonist (IL-1ra).[165]

Similarly, the evidence supporting the role of TNF-α in the mechanisms of preterm parturition includes: (1) TNF-α stimulates prostaglandin production by amnion, decidua, and myometrium;[8] (2) human decidua can produce TNF-α in response to bacterial products;[166,167] (3) amniotic fluid TNF-α bioactivity and immunoreactive concentrations are elevated in women with preterm labor and intra-amniotic infection;[166] (4) in women with preterm PROM and intra-amniotic infection, TNF-α concentrations are higher in the presence of labor;[168] (5) TNF-α can induce preterm parturition when administered systemically to pregnant animals;[48,169,170] (6) TNF-α can stimulate the production of MMPs,[171,172] which may play a role in membrane rupture[173–175] and cervical ripening;[171,176,177] and (7) TNF-α application in the cervix induces changes that resemble cervical ripening.[178]

Redundancy in the cytokine network: Additional cytokines [(IL-6,[86,179–183] IL-10,[163,184,185] IL-16,[186] IL-18,[187] colony stimulating factors (CSFs),[188–190] macrophage migration inhibitory factor (MIF)[191]] and chemokines [IL-8,[189,192–194] monocyte chemotactic protein-1 (MCP-1),[195] epithelial cell-derived neutrophil-activating peptide-78,[196] and Regulated on Activation Normal T cell Expressed and Secreted (RANTES)[197]] had also been implicated in the mechanisms of disease in preterm labor and delivery. The redundancy of the cytokine network implicated in parturition is such that a blockade on a single factor is insufficient to prevent preterm delivery in the context of infection. For example, preterm labor can occur in knockout (KO) mice for the IL-1 type I receptor after exposure to infection, suggesting that IL-1 is sufficient, but not necessary, for the onset of parturition in the context of intraamniotic infection/inflammation.[198] However, blockade of both IL-1 and TNF-α production in a double-KO mouse model has been associated with a decreased rate of preterm birth after infection.[199]

Anti-inflammatory cytokines and preterm labor: Interleukin-10 is thought to be a key cytokine for the maintenance of pregnancy. Indeed, IL-10 production is significantly reduced in the placenta of patients at term not in labor compared with that from first- and second-trimester tissues, suggesting that down-regulation of IL-10 is a physiologic event that favors an inflammatory state around the time of onset of labor.[184] IL-10 has also been implicated in the control of preterm parturition associated with inflammation.[185] Indeed, IL-10 expression was reduced in placental tissues of pregnancies complicated by preterm labor and chorioamnionitis when compared to placental tissues from normal controls.[185]

Importantly, IL-10 inhibited COX-2 mRNA expression in cultured placental explants from preterm labor deliveries, but not in those from labor at term, indicating that the mechanisms involved in the regulation of the inflammatory response during term and preterm parturition may be different.[185] Further evidence that IL-10 plays a role in down-regulation of the inflammatory response in preterm labor comes from a study in which pregnant rhesus monkeys (n=13) were allocated to three interventional groups: (1) intra-amniotic IL-1β infusion with maternal dexamethasone intravenously (n = 4), (2) intra-amniotic IL-1β + interleukin-10 (n = 5), and (3) intra-amniotic IL-1β administered alone (n = 5). Dexamethasone and interleukin-10 treatment significantly reduced IL-1β-induced uterine contractility ($P<0.05$) Tumor necrosis factor-alpha levels and leukocyte counts were also attenuated by interleukin-10 treatment ($P <0.05$).[163] The administration of IL-10 in animal models of infection has been associated with improved pregnancy outcome.[200,201]

Inflammation and fetal injury: the fetal inflammatory response syndrome

While the traditional definition of inflammation describes “localized inflammation” to a particular tissue, it is now recognized that inflammation may be present in circulating blood. Such a state is referred as the “Systemic Inflammatory Response Syndrome.” This condition was originally described in adults and is often referred to by the acronym “SIRS.” SIRS was introduced in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine to describe a complex set of findings, which often involved cardiovascular abnormalities thought to be the result of systemic activation of the innate immune system.[202] The changes, which included fever, tachycardia, hyperventilation, and an elevated white blood cell count,[202] have been attributed to the effects of cytokines and other pro-inflammatory mediators.[203] In 2001, the same organization noted that the elevation of certain mediators, such as IL-6, may be associated with SIRS and that this observation may bring about a new definition of the syndrome in adult patients, as the clinical and laboratory findings originally proposed to characterize SIRS were non-specific.[204] We defined the fetal counterpart of SIRS for the first time in 1997, using precisely the same parameter that was proposed in adults: an elevated IL-6 concentration (in fetal blood).[205] We coined the term, “Fetal Inflammatory Response Syndrome” (FIRS) to refer to the fetal counterpart of SIRS.[9]

FIRS was originally described in pregnancies complicated by preterm labor and preterm PROM and was operationally defined as a fetal plasma concentration of IL-6 > 11 pg/ml. Fetuses with FIRS had a higher rate of severe neonatal morbidity (respiratory distress syndrome, suspected or proved neonatal sepsis, pneumonia, bronchopulmonary dysplasia. intraventricular hemorrhage, periventricular leukomalacia, or necrotizing enterocolitis)[9] and a shorter cordocentesis-to-delivery interval.[9,10]

The original work describing FIRS was based on fetal blood samples obtained by cordocentesis.[9,10] Many of the findings have since been confirmed by studying umbilical cord blood at the time of birth, including the elevation of pro-inflammatory cytokines and the relationship between these cytokines and the likelihood of clinical and suspected sepsis.[206–208] Pathological examination of the umbilical cord is an alternative approach to determine whether fetal inflammation was present before birth. Funisitis and chorionic vasculitis are the histopathologic hallmarks of FIRS.[209] Funisitis is associated with

endothelial activation, a key mechanism in the development of organ damage,[210] and neonates with funisitis are at increased risk for neonatal sepsis[20] and long-term handicaps, such as bronchopulmonary dysplasia (BPD)[206] and cerebral palsy.[211] Another approach to detect FIRS is to measure C-reactive protein concentration in umbilical cord blood, which has been shown to be elevated in patients with amniotic fluid infection, funisitis, and congenital neonatal sepsis.[212] In addition, since neutrophils in the amniotic fluid are predominantly of fetal origin,[213] the amniotic fluid white blood cell count can also be used as an indirect index of fetal inflammation.[213] Intra-amniotic inflammation is a risk factor for impending preterm delivery and adverse perinatal outcome in women with preterm PROM, even in the absence of documented intra-amniotic infection.[214]

Fetal target organs during FIRS

Fetal microbial invasion or other insults can result in a systemic fetal inflammatory response that can progress toward multiple organ dysfunction, septic shock, and perhaps death in the absence of timely delivery. Evidence of multisystemic involvement in cases of FIRS includes increased concentrations of fetal plasma MMP-9,[215] an enzyme involved in the digestion of type IV collagen and in the pathophysiology of preterm PROM.[175] Moreover, several fetal organs including the hematopoietic system, the adrenals, heart, brain, lungs, and skin have been proposed to be target organs during FIRS (Figure 2).

The hematopoietic system: The hematological response of the human fetus with FIRS is characterized by significant changes in the granulocyte and red blood cell lineages.[216] Indeed, two-thirds of fetuses with FIRS have neutrophilia, defined as a neutrophil blood count above the 95th percentile for the gestational age.[216] In contrast, only 7.1% of these fetuses (3/42) had neutropenia.[216] The mechanisms responsible for fetal neutrophilia are not completely understood. However, it has been proposed that Granulocyte Colony Stimulating Factor (G-CSF), the primary physiologic regulator of neutrophil production, may participate in these mechanisms.[217] Indeed, fetuses with FIRS had a higher median plasma concentration of G-CSF than those without FIRS (median: 714.4 pg/ml, range: 23.3–4229.2 vs. median: 55.7 pg/ml, range: 7.7–411; $p<0.01$).[217]

Fetuses with FIRS had a higher median nucleated red blood cell count than those without FIRS (median count: 2.42, range: 0–35 vs. median count: 1.38, range: 0–63.6; $p<0.05$).[216] These changes are not associated with changes in the umbilical vein pH or PO_2 levels.[218] Thus, metabolic acidemia is unlikely to be the cause of these hematological changes, as described in fetuses with intrauterine growth restriction and abnormal Doppler velocimetry in the middle cerebral artery, inferior vena cava, and ductus venosus.[219] Thus, the possibility that elevated nucleated red blood cell counts are a consequence of FIRS should be considered. Evidence in favor of this has been recently reported, indicating that the IL-6 concentration in umbilical cord blood may be an independent explanatory variable for the prediction of high nucleated red blood cell count.[220]

FIRS has also been associated with changes in markers of monocyte and neutrophil activation.[221] Indeed, fetuses that were delivered within 72 hours of cordocentesis had a higher expression of CD11c, CD13, CD15, and CD67 than those delivered at term. In

contrast, there were no significant differences in the percentages of CD14 and CD63 between the two groups. Collectively, these results indicate that fetuses destined to deliver prematurely have phenotypic evidence of activation of the monocyte-neutrophil system.[221]

The fetal thymus: Thymus involution has been associated with infection in neonates. Recent evidence indicates that this also is the case in the fetus. A sonographically small thymus is found in cases with intra-amniotic infection/inflammation among patients with preterm labor and intact membranes.[222] Indeed, the fetal thymus perimeter measured <5th percentile for gestational age in all cases with microbial invasion of the amniotic cavity (10/10), but in only 23.8% (5/21) of cases with negative cultures ($P < 0.01$). Furthermore, the fetal thymus was <5th percentile for gestational age in 100% (8/8), 71.4% (5/7), and 12.5% (2/16) of fetuses with funisitis, isolated chorioamnionitis, and without histologic signs of infection, respectively. Depletion of thymocytes probably results from glucocorticoid-induced apoptosis of the lymphoid tissue during the acute phase response.[223] Thus, thymic involution has been proposed to be the result of lymphocyte depletion from both the thymic cortex and medulla, possibly mediated by activation of the hypotalamo-pituitary-adrenal axis.[223]

The adrenal glands: Fetuses with FIRS have endocrine evidence of "stress" expressed as an abnormal cortisol/dehydroepiandrosterone ratio.[224] Indeed, Yoon et al.[224] reported a significant correlation between fetal plasma cortisol and fetal plasma interleukin-6 ($r = 0.3$, $p<0.05$) and a significant association between fetal plasma cortisol/dehydroepiandrosterone sulfate ratio and a shorter interval from cordocentesis to delivery (hazards ratio: 2.9, 95% CI: 1–8.4; $p<0.05$). Fetal plasma cortisol, but not maternal cortisol, was an independent predictor of the duration of pregnancy, after adjusting for gestational age and the results of amniotic fluid cultures (hazard ratio: 2.9, 95% CI: 1.3–6.7; $p<0.05$). Patients with preterm PROM who went into spontaneous labor and delivered within 7 days of cordocentesis had a significantly higher median fetal plasma concentration of cortisol but not of dehydroepiandrosterone sulfate than those delivered after 7 days (for fetal plasma cortisol: median 8.35 μg/dl, range: 4.7 to 12.4 μg/dl vs. median 4.75 μg/dl, range: 3.0 to 10.4 μg/dl; $p<0.0001$; for fetal plasma dehydroepiandrosterone sulfate: median 154.4 μg/dl, range: 8.6 to 333.8 μg/dl vs. median 194.6 μg/dl, range: 96.7 to 402.5 μg/dl; $p=0.09$).[224] Collectively, these results indicate that an elevation in fetal plasma cortisol, but not dehydroepiandrosterone sulfate (DHEA-S), was followed by the onset of spontaneous preterm labor in patients with preterm PROM. Adult patients admitted to an intensive care unit with burns[225] or pancreatitis have elevation of the cortisol/DHEA-S ratio just as human fetuses with FIRS. This may have short and long term implications given recent observations about the effect of glucocorticoids in fetal programming of several metabolic functions.[226–229]

The fetal skin: The fetal skin is also a target organ during FIRS. Indeed, Kim et al[230] studied the expression of TLR-2 and TLR-4 skin samples from fetuses between 21 to 24 weeks of gestation and reported that: 1) the skin from fetuses born to mothers without chorioamnionitis expressed TLR-2 and TLR-4 in the epidermis (TLR-2: median 3%, range 0.4%−7.2% and TLR-4: median 99.5%, range 91%−100%); 2) there was a dramatic increase

in the expression of TLR-2, but not in TLR-4, in the epidermis of fetuses born after chorioamnionitis (TLR-2: median 19.6%, range 10.3%−89.6%; p=0.007 and TLR-4: median 100%, range 89.4%−100%; p=0.5); and 3) TLR-2 and TLR-4 were also expressed in the mononuclear inflammatory infiltrate of the dermal-epidermal junction. The authors proposed that the fetal skin is capable of recognizing the presence of microorganisms through the expression of ‘‘pattern-recognition receptors’’ and, thus, participates in a fetal inflammatory response to microbial products.[230] The clinical manifestation of the involvement of the fetal skin during FIRS would be a fetal dermatitis.

The fetal kidneys: Yoon et al. [231] reported that oligohydramnios is associated with FIRS among patients with preterm PROM. Indeed, patients with an amniotic fluid index ≤ 5 cm had: 1) significantly higher IL-6 concentrations in umbilical cord plasma at birth (fetal response); 2) higher concentrations of amniotic fluid pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α (intra-amniotic inflammatory response); and 3) higher rates of histologic and clinical chorioamnionitis (maternal response) than did those with an amniotic fluid index > 5 cm.[224,231] These observations are consistent with the report that fetuses with fetal bacteremia diagnosed by cordocentesis had oligohydramnios (amniotic fluid index < 5 cm) more frequently than did those with a sterile blood culture.

The reasons why oligohydramnios in preterm PROM is associated with a higher rate of fetal infection/inflammation remain unclear. Yoon et al.[224,231] proposed that, since the amniotic fluid has antimicrobial properties,[232,233] oligohydramnios may reduce the protective effect of this component of innate immunity. Alternatively, redistribution of blood flow away from the kidneys may take place as part of the host response to microbial products, leading to oligohydramnios.

The fetal heart: A recent report indicates that fetuses with preterm PROM have changes in the parameters used to evaluate diastolic function of the heart when compared to fetuses of women with uncomplicated pregnancies.[234] The changes in the Doppler waveform characteristics in fetuses with preterm PROM are consistent with a high left ventricular compliance, particularly among those with proven intra-amniotic infection. These changes include a higher ratio between the early filling delta E/A ratio in both ventricles and a higher delta E/A VTI in the left ventricle, as compared to normal fetuses. The E wave reflects early diastolic filling, while the A wave represents changes in flow velocity due to atrial contraction. It is possible that these changes represent a compensatory mechanism similar to that observed in adults with sepsis. It is also possible that fetuses unable to change cardiac compliance in the context of a fetal systemic inflammatory response syndrome may not be able to maintain ventricular stroke volume and cardiac output and, hence, may not perfuse the brain adequately, predisposing to hypotension and brain ischemia in utero, which could create conditions for the development of periventricular leukomalacia. These changes in diastolic function may, therefore, have protective and even survival value. In cases of overwhelming fetal sepsis (the pathophysiologic counterpart to septic shock in adults), myocardial depression may lead to fetal death, which we have observed in cases with preterm PROM. The mechanism by which sepsis induces myocardial depression is not completely understood. The most likely explanation is that the myocardium is depressed by

the action of soluble factors such as bacterial products and cytokines, which are elevated in the circulation of patients with septic shock.[235–237]

The observation that fetuses with preterm PROM and intra-amniotic infection undergo changes in cardiac function are consistent with the findings of Yanowitz et al.,[238] who reported that neonates born with histologic chorioamnionitis had several hemodynamic abnormalities, including a decreased mean and diastolic blood pressure, and that there was a correlation between mean blood pressure and umbilical cord IL-6 concentrations.[238] It is possible that some of these hemodynamic changes are present in utero and may contribute to the pathophysiology of periventricular leukomalacia and cerebral palsy.[239] Those conditions were originally considered to be due to ischemia/hypoxia and have recently been linked to chorioamnionitis, infection, and fetal inflammation. In the context of FIRS, the combination of inflammatory changes in the brain and fetal systemic hypotension may increase the likelihood of brain injury. Recent evidence in support of this view is the observation that histologic chorioamnionitis with histologic evidence of placental hypoperfusion (poorly vascularized villi, multiple capillary lumina is some villi, increased intervillous volume and reduced total capillary bed) is associated with and an OR of 15.2 95% CI: 1.3–181) to have abnormal neurological outcome at the corrected age to 24 months.[240]

Why does the fetus mount an inflammatory response?

When the fetal inflammatory response syndrome was first described, we proposed that in the context of intrauterine infection, the onset of preterm labor would have survival value and that it would be part of the repertoire of host defense mechanisms against infection.[9,10] The fetus would use the effector limb of the immune response via the secretion of pro-inflammatory cytokines to signal the onset of labor and exit a hostile intrauterine environment. Evidence in support of this hypothesis has been recently reported by Lahra et al.,[241] who compared the frequency of a histological fetal response to chorioamnionitis (umbilical vasculitis with or without funisitis) between infants who survived the neonatal period and cases of perinatal death. Neonatal survivors had a higher prevalence of histological chorioamnionitis (95% CI, 1.02–1.21; p=0.02) and a higher rate of umbilical vasculitis/funisitis at 25 to 29 weeks of gestation (95% CI, 0.33–0.86; p=0.01) and 30 to 34 weeks of gestation (95% CI, 0.18–0.85; p=0.02), when compared to those who died in the perinatal period.

Important long-term consequences of FIRS include chronic lung disease[193,194,242–245] and cerebral palsy.[117,211,246–249] The readers are referred to the original articles and reviews regarding these transcendental consequences of FIRS.

A role of the fetus in the onset of labor

Among women with preterm PROM, FIRS is associated with the impending onset of preterm labor, regardless of the inflammatory state of the amniotic fluid (Figure 3).[9] This suggests that the human fetus plays a role in initiating the onset of labor. However, maternal cooperation must occur for parturition. Thus, it is possible that systemic fetal inflammation may occur in the absence of labor when the inflammatory process does not involve the chorioamniotic membranes and decidua. Such instances may occur in the context of

hematogenous viral infections (i.e. CMV infection) or other disease processes (i.e., alloimmunization).

Fetal death and maternal/fetal systemic inflammation

The rate of maternal inflammation is nine times more frequent than that of fetal inflammation in stillbirth. This could have two potential explanations. First, it is possible that fetal infection occurs, but fails to trigger a fetal inflammatory response and the onset of preterm labor. In this case, *in utero* fetal death would represent failure of the host response mechanisms dealing with intrauterine infection. This concept is supported by evidence that, in some cases of intrauterine death due to group B streptococci (with intact membranes), there may be absence of both a maternal and a fetal inflammatory response despite widespread fetal infection.[250,251] Similar observations can be derived from the study of Tafari and colleagues with intrauterine infection by *Ureaplasma urealyticum*.[252] Despite the fact that intrauterine infection was documented by culture of micro-organisms from fetal lung tissue at postmortem examination, fetal death could occur before the onset of labor. The second possible explanation for the discrepant rate of maternal and fetal inflammatory responses is that inflammation of the placental membranes may occur after fetal death and be etiologically unrelated to the fetal demise.[253] The possibility that fetal death represent a failure of host defense requires further consideration given the association between homozygosity for the IL-1 receptor antagonist (IL-1ra) allele 2 and the risk of fetal death.[254] Carriage of this allele is associated with increased production of IL-1ra.[255,256] An excess of IL-1ra in the fetal compartment may limit the ability of the fetus to deploy a pro-inflammatory response and thus limit the repertoire of mechanisms available for host defense, including the ability to exit a hostile intrauterine environment by initiating the onset of labor.[9,10,257] However, further studies are required to test this hypothesis.

The maternal systemic inflammatory response in normal pregnancy and preterm labor and delivery

Normal pregnancy has been proposed to be a state of physiologic activation of the innate limb of the immune response. Evidence in support of this view is the observation that normal pregnancy is associated with phenotypic changes in monocytes and granulocytes, as demonstrated by flow cytometry studies showing that granulocytes from normal pregnant women have up-regulation of CD14 (receptor for lipopolysaccharide and its binding protein) and CD64 (high affinity receptor for IgG, mediating the release of IL-1, IL-6 and TNF-α), and down-regulation of CD16 (low affinity receptor for aggregated IgG) and HLA-DR (class II MCH antigen) than granulocytes of nonpregnant women.[258] Similarly, monocytes from pregnant women had up-regulation of CD11b (integrin αM subunit that binds to ICAM-1), CD14, CD18 (Integrin β2 subunit that mediates fir adhesion of leukocytes to endothelium), CD62L (L-selectin, that mediates tethering and rolling of leukocytes), and CD64), and down-regulation of HLA-DR.[258] Moreover, baseline iROS, oxidative burst and stimulation index values are increased in both granulocytes and monocytes.[258]

Preterm parturition with intact or rupture membranes is associated with phenotypic and metabolic changes in maternal monocytes and granulocytes that are consistent with the presence of intravascular maternal inflammation.[259,260] Indeed, preterm labor and intact

membranes is associated with up-regulation of CD11b, CD15 (fucosylated carbohydrate structure, recognizes endothelial selectins) and CD66 in maternal granulocytes, as well as up-regulation of CD11b and CD15 in maternal monocytes.[259] Similarly, preterm PROM is associated with up-regulation of CD11b, CD14, CD64 and CD66b on granulocytes and CD11b on monocytes.[260] Moreover, both preterm labor with intact membranes and preterm PROM were associated with increased ratio of oxidative burst over basal intracellular oxygen radical species in both granulocytes and monocytes.[259,260]

Conclusions

The evidence reviewed in this article indicates that intraamniotic infection/inflammation is causally linked to preterm parturition, fetal injury, and the development of a fetal inflammatory response syndrome, in a subset of patients. Moreover, preterm parturition (with intact or ruptured membranes) is associated with a maternal systemic inflammatory response characterized by phenotypic and metabolic changes of maternal monocytes and granulocytes. It is possible that modulation of inflammation with anti-inflammatory cytokines (i.e. IL-10), corticoids, antioxidants and/or other factors, such as anti-MIF antibodies, may complement antibiotic therapy and limit fetal injury.

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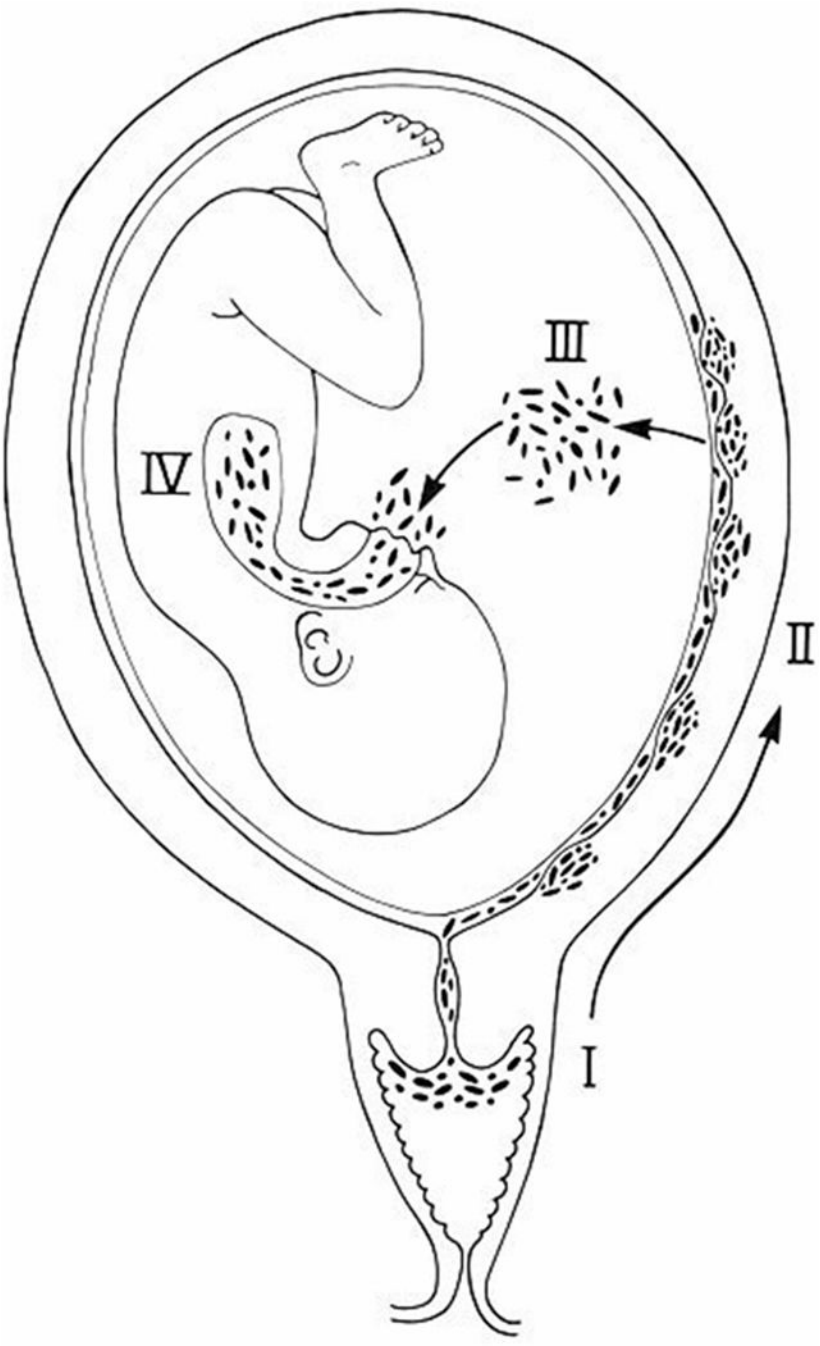

Figure 1.

The most common pathway of intrauterine infection is the ascending route. (Reproduced, with permission, from Romero R, Mazor M. Infection and preterm labor. Clin Obstet Gynaecol 1982; 9:593–607).

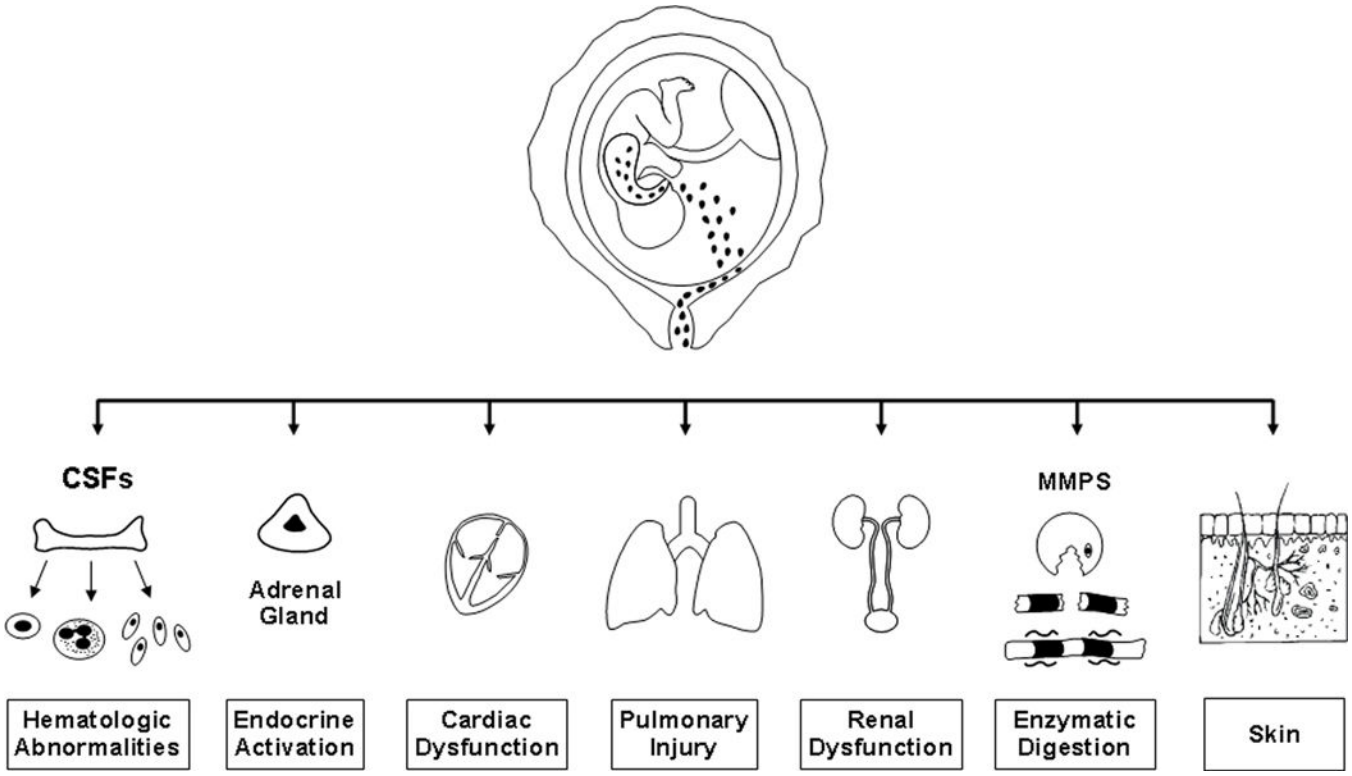

Figure 2.

Fetal target organs during the fetal inflammatory response syndrome. CSFs, colony-stimulating factors; MMPs, matrix metalloproteinases.

		n	Procedure-to-Delivery Interval (median, range, days)
I	AF IL-6 ≤ 7.9 ng/ml FP IL-6 ≤ 11 pg/ml	14	5 (0.2-33.6)
II	AF IL-6 > 7.9 ng/ml FP IL-6 ≤ 11 pg/ml	5	7 (1.5-32)
III	AF IL-6 > 7.9 ng/ml FP IL-6 > 11 pg/ml	6	1.2 (0.25-2)
IV	AF IL-6 ≤ 7.9 ng/ml FP IL-6 > 11 pg/ml	5	0.75 (0.13-10)

Figure 3.

Classification and procedure-to-delivery intervals of patients according to amniotic fluid and fetal plasma interleukin-6 (IL-6) concentrations. A white color in the fetal or amniotic fluid (AF) compartment represents a low fetal plasma (FP) or amniotic fluid IL-6 concentration, respectively. Black in the fetal or amniotic fluid compartment denotes elevated fetal plasma or amniotic fluid IL-6 concentration.