# Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance

Chong Jai Kim, MD, PhD; Roberto Romero, MD, DMedSci; Piya Chaemsaithong, MD; Noppadol Chaiyasit, MD; Bo Hyun Yoon, MD, PhD; Yeon Mee Kim, MD

Acute inflammatory lesions of the placenta consist of diffuse infiltration of neutrophils at different sites in the organ. These lesions include acute chorioamnionitis, funisitis, and chorionic vasculitis and represent a host response (maternal or fetal) to a chemotactic gradient in the amniotic cavity. While acute chorioamnionitis is evidence of a maternal host response, funisitis and chorionic vasculitis represent fetal inflammatory responses. Intraamniotic infection generally has been considered to be the cause of acute chorioamnionitis and funisitis; however, recent evidence indicates that "sterile" intraamniotic inflammation, which occurs in the absence of demonstrable microorganisms induced by "danger signals," is frequently associated with these lesions. In the context of intraamniotic infection, chemokines (such as interleukin-8 and granulocyte chemotactic protein) establish a gradient that favors the migration of neutrophils from the maternal or fetal circulation into the chorioamniotic membranes or umbilical cord, respectively. Danger signals that are released during the course of cellular stress or cell death can also induce the release of neutrophil chemokines. The prevalence of chorioamnionitis is a function of gestational age at birth, and present in 3—5% of term placentas and in 94% of pacentas delivered at 21-24 weeks of gestation. The frequency is higher in patients with spontaneous labor, preterm labor, clinical chorioamnionitis (preterm or term), or ruptured membranes. Funisitis and chorionic vasculitis are the hallmarks of the fetal inflammatory response syndrome, a condition characterized by an elevation in the fetal plasma concentration of interleukin-6, and associated with the impending onset of preterm labor, a higher rate of neonatal morbidity (after adjustment for gestational age), and multiorgan fetal involvement. This syndrome is the counterpart of the systemic inflammatory response syndrome in adults: a risk factor for short- and long-term complications (ie, sterile inflammation in fetuses, neonatal sepsis, bronchopulmonary dysplasia, periventricular leukomalacia, and cerebral palsy). This article reviews the definition, pathogenesis, grading and staging, and clinical significance of the most common lesions in placental disease. Illustrations of the lesions and diagrams of the mechanisms of disease are provided.

**Key words:** chorionic vasculitis, CXCL6, fetal inflammatory response syndrome, granulocyte chemotactic protein, interleukin (IL)-8, microbial invasion of the amniotic cavity, placental pathology, pregnancy, prematurity, preterm, staging, sterile inflammation

Acute chorioamnionitis is the most frequent diagnosis in placental pathology reports and is generally considered to represent the presence of intraamniotic infection or "amniotic fluid infection syndrome."[1-10] Yet, acute chorioamnionitis can occur in the setting of "sterile intraamniotic inflammation" in the absence of demonstrable microorganisms and is induced by "danger signals" released under conditions of cellular stress, injury, or death.[11-15] Therefore, acute chorioamnionitis is evidence of intraamniotic inflammation and not necessarily intraamniotic infection. The characteristic morphologic feature of acute chorioamnionitis is diffuse infiltration of neutrophils into the chorioamniotic membranes.[9] Since obstetricians use the term *chorioamnionitis* to refer to a clinical syndrome (the combination of fever, maternal or fetal tachycardia, uterine tenderness, foul-smelling amniotic fluid) frequently associated with "acute chorioamnionitis" on microscopic examination of the placenta, the word *histologic* has been introduced into the medical lexicon to specify the differences between the clinical syndrome, clinical chorioamnionitis, and the pathologic diagnosis *of acute*

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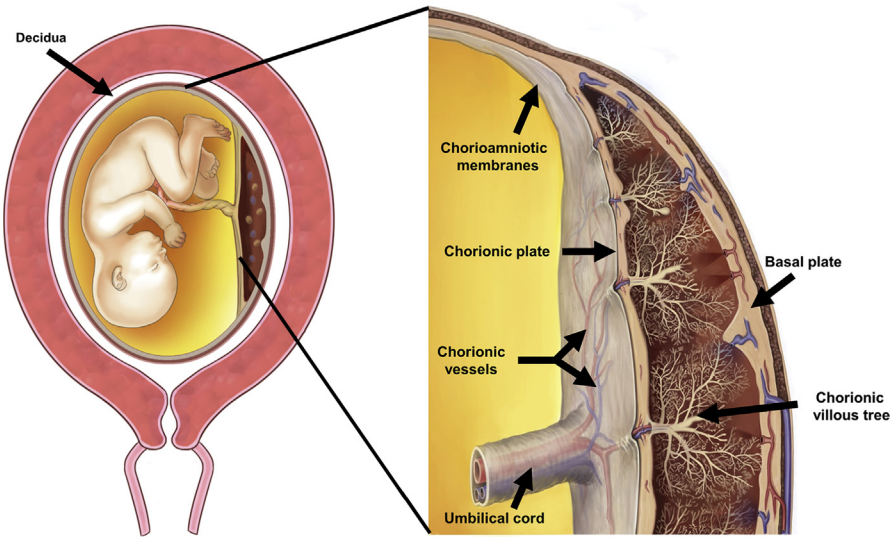
FIGURE 1
**The anatomy of the pregnant uterus with an emphasis on the placenta**




The **left side** of the illustration shows the fetus, umbilical cord, and placenta. The chorioamniotic membranes include the amnion and chorion. Decidua is the pregnant endometrium. The **right side** of the illustration shows a cross-section of the human placenta, which includes the chorionic plate, chorioamniotic membranes, umbilical cord, and the intervillous space. The basal plate of the placenta is traversed by the spiral arteries, which bring maternal blood into the intervillous space. The villous circulation (fetal) is illustrated in a cross-section of the stem villi. The fetal vessels on the surface of the chorionic plate include arteries and veins, which coalesce to form the umbilical vein and umbilical arteries.

Modified from Benirschke K, et al.[5] Infectious disease. In: Pathology of the human placenta, 6th ed. Berlin: Springer, 2012, 33.

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*chorioamnionitis*. These terms are not synonymous, and confusion occurs when they are used interchangeably. Herein, the term *acute chorioamnionitis* will refer to "acute histologic chorioamnionitis" given the focus of this article is the pathologic condition rather than the clinical syndrome. We will review the acute inflammatory responses deployed by the mother and fetus in response to inflammatory stimuli within the amniotic cavity.

TABLE 1
**Frequency of chorioamnionitis according to gestational age at delivery**

| Weeks of gestation | Chorioamnionitis, n | Total no. of patients | Percentage |
|---|---|---|---|
| 21–24 | 17 | 18 | 94.4 |
| 25–28 | 19 | 48 | 39.6 |
| 29–32 | 34 | 96 | 35.4 |
| 33–36 | 53 | 497 | 10.7 |
| 37–40 | 233 | 6139 | 3.8 |
| 41–44 | 36 | 707 | 5.1 |
| TOTALS | 392 | 7505 | 5.2 |

Modified from Russell P.[2]

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## Definition

The placenta is composed of three major structures: the placental disc, the chorioamniotic membranes, and the umbilical cord (Figure 1). Acute inflammatory lesions of the placenta are characterized by the infiltration of neutrophils in any of these structures.[9] Specifically, when the inflammatory process affects the chorion and amnion, this is termed acute chorioamnionitis[9]; if it affects the villous tree, this represents acute villitis.[9] If the inflammatory process involves the umbilical cord (umbilical vein, umbilical artery, and the Wharton's jelly), this is referred to as acute funisitis, the histologic counterpart of the fetal inflammatory response syndrome (FIRS; Figure 1).[16]

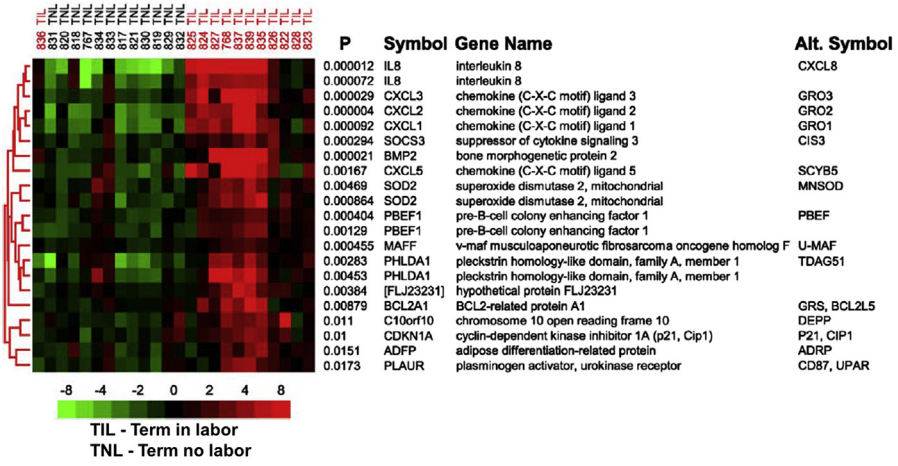
## Prevalence of acute chorioamnionitis

Table 1 shows the frequency of acute chorioamnionitis as a function of gestational age at delivery in a study of 7505 placentas from singleton pregnancies that were delivered after 20 weeks of gestation.[2] It is noteworthy that the frequency of acute chorioamnionitis in patients who delivered between 21-24 weeks of gestation was 94.4% (17/18 patients).[2] This is consistent with multiple studies subsequently reported by our group[17] and others[18-20] and emphasizes the role of acute inflammation in early preterm deliveries and midtrimester spontaneous abortions.

Acute chorioamnionitis is observed more frequently in the placentas of women who delivered after spontaneous labor at term than in the absence of labor[21,22] (early labor with cervical dilation of <4 cm, 11.6% [10/86] vs no labor, 4.4% [34/775]; $P < .01$).[22] Moreover, the longer the duration of labor and cervical dilation of >4 cm, the higher the frequency of acute chorioamnionitis (active labor, 30.4% [7/23] vs early labor, 11.6% [10/86]; $P < .05$).[23] This observation has two possible explanations: first, the frequency of microbial invasion of the amniotic cavity is higher in women in spontaneous labor at term with intact membranes than in those without labor (17% vs 1.5%).[24] Alternatively, labor per se is an

inflammatory state, as demonstrated by the study of the gene expression profile of the chorioamniotic membranes.[25] The chorioamniotic membranes obtained from women who experienced labor (even in the absence of any detectable acute chorioamnionitis) overexpressed neutrophil-specific chemokines (chemokine [C-X-C motif] ligand 1 [CXCL1], CXCL2, and interleukin [IL]-8) and monocyte-specific chemokines (C-C motif ligand 3 [CCL3], macrophage inflammatory protein [MIP]-1$\alpha$, CCL4 [MIP-1$\beta$], and CCL20 [MIP-3$\alpha$]; Figure 2).[25] This is consistent with reports that the amniotic fluid concentrations of chemokines such as IL-8,[26] monocyte chemotactic protein (MCP)-1,[27] growth-regulated oncogene (GRO)-$\alpha$,[28] MIP-1$\alpha$,[29] and cytokines such as IL-1[30-32] and IL-6[33,34] are higher in women at term in spontaneous labor than in those not in labor.

FIGURE 2
**Spontaneous labor at term is an inflammatory phenomenon**




The gene expression (mRNA) profile of the chorioamniotic membranes of women not in labor at term was compared to that of membranes obtained from women who had undergone labor. Patients with histologic inflammation of the amnion and chorion were excluded. The figure represents hierarchical clustering in which patients not in labor are labeled as "TNL" (black letters at the top of the figure), while those in labor are labeled as "TIL" (red letters at the top of the figure). Columns correspond to patients; rows correspond to the most discriminant microarray probe sets. The magnitude of expression changes (fold change) are coded in the color key. Most of the differentially-expressed genes shown in the figure are involved in inflammation (chemokines, cytokines). This is evidence that examining global gene expression (unbiased) indicates that inflammation-related molecules are overexpressed in labor.

Modified from Figure 2 in Haddad R, et al.[25]

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## Pathology

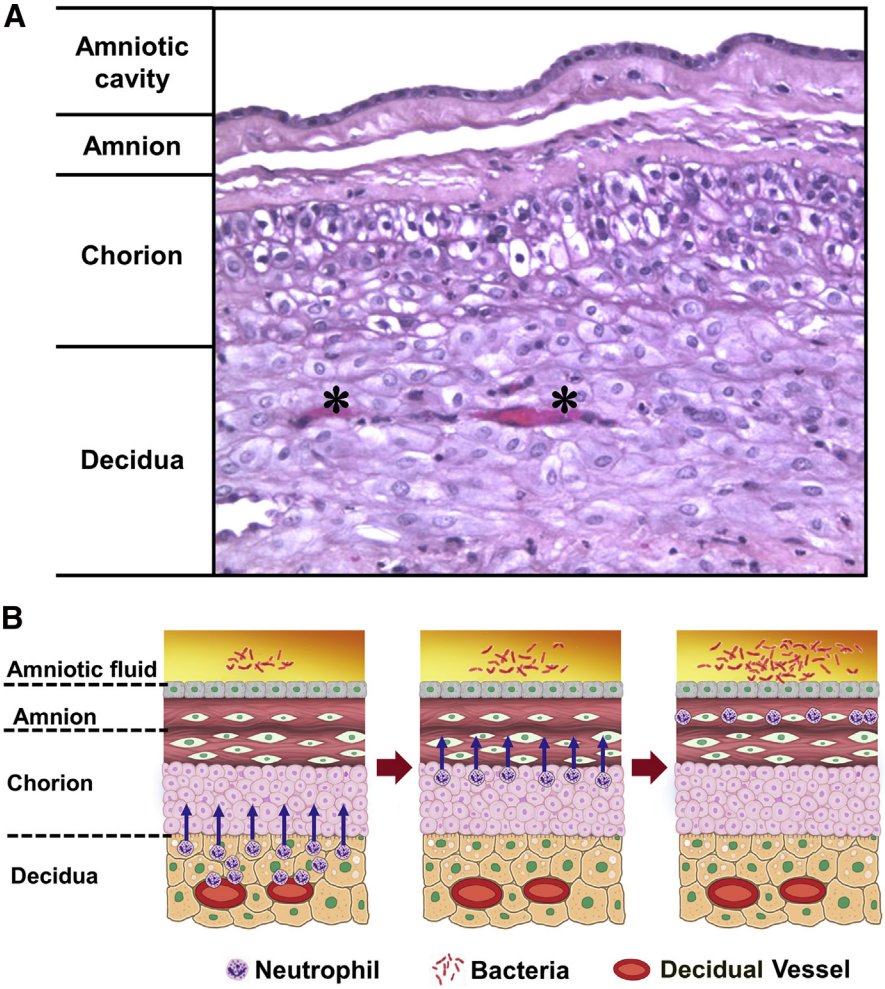
The placenta is considered to be the apposition or fusion of the fetal membranes/placental disc to the uterine mucosa (decidua) for physiologic exchange.[35] The decidua is of maternal origin; the chorioamniotic membranes and villous tree are of fetal origin. Thus, the precise origin of the inflammatory process (maternal vs fetal) can be determined by whether infiltrating neutrophils are of maternal or fetal origin.

Neutrophils are not normally present in the chorioamniotic membranes and migrate from the decidua into the membranes in cases of acute chorioamnionitis (Figure 3).[36,37] On the other hand, maternal neutrophils normally circulate in the intervillous space (Figure 1). When there is a chemotactic gradient, neutrophils migrate toward the amniotic cavity, neutrophils in the intervillous space mobilize into the chorionic plate of the placenta, which is normally devoid of these cells. Thus, inflammation of the chorionic plate, except chorionic vasculitis, is also a maternal inflammatory response.

Neutrophils in acute chorioamnionitis are of maternal origin. Fluorescence in situ hybridization (FISH) with probes for X and Y chromosomes performed in cytospin slides of placentas from male fetuses showed that approximately 90% of neutrophils derived from the membranes were of maternal origin.[36] Subsequently, FISH combined with immunohistochemistry for CD45 (to identify leukocytes) demonstrated that CD45 positive cells in the chorionic membranes were of maternal origin.[37] In contrast, inflammation of the umbilical cord and the chorionic vessels on the chorionic plate of the placenta is of fetal origin.[38] This conclusion is largely based on the understanding of the anatomy of these tissues, because neutrophils invading the walls of the umbilical vein and arteries must migrate from the fetal circulation to enter the walls of these vessels (Figure 4). Insofar as the origin of white blood cells in the amniotic fluid in cases of intraamniotic inflammation, the only study reported to date for cases of intrauterine infection with intact membranes suggested that 99% of neutrophils are of fetal origin.[39]

Inflammation of the umbilical vessels begins in the vein (phlebitis) and is followed by involvement of the arteries (arteritis). Infiltration of neutrophilis into the Wharton's jelly is common in acute funisitis.[40] The molecular pathogenesis of funisitis has been studied with the use of microarray analysis followed by quantitative real-time polymerase chain reaction (PCR) obtained from micro-dissected umbilical arteries and veins. The expression of IL-8 messenger RNA (mRNA; the prototypic neutrophil chemokine) is higher in the umbilical vein than in the umbilical artery.[40] Moreover, there are substantial differences in the genes expressed by the walls of the umbilical artery and vein. The pattern of gene expression suggests that the wall of the umbilical vein is more prone to a proinflammatory response

FIGURE 3
**Migration of the neutrophils from the decidual vessels into the chorioamniotic membranes**




**A,** Normal histology of the chorioamniotic membranes, which are composed of amnion and chorion laeve. The decidua is adjacent to the chorion and contains maternal capillaries (*black asterisks*). Neutrophils migrate from the maternal circulation in the presence of chemotactic gradient (increased amniotic fluid neutrophil chemokine concentrations). **B,** Migration of neutrophils from the decidual vessels (*red*) towards the amnion (indicated by upward-pointing arrows). The location of bacteria is within the amniotic cavity. Initially, neutrophils are in the decidua (**left**); however, in subsequent stages, invade the chorion (**center**) and amnion (**right**).

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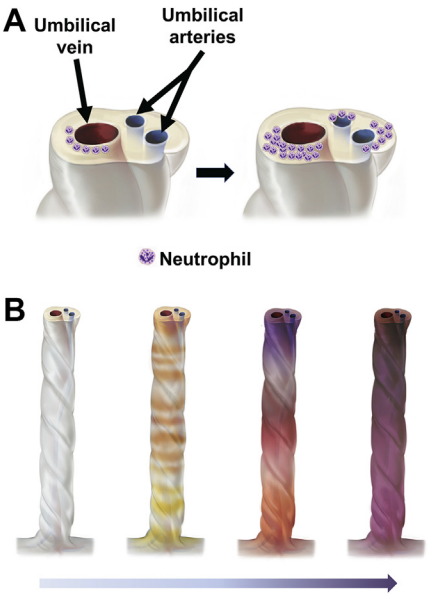
FIGURE 4
**Topography of the inflammatory process in the umbilical cord**




**A,** Typically, acute funisitis begins as inflammation of the umbilical vein (umbilical phlebitis; the *red vessel* represents the umbilical vein), followed by umbilical arteritis involving the umbilical arteries (*blue*). **B,** Progression of inflammation along the length of the umbilical cord. The initial phase is multifocal, as demonstrated by the *yellow/orange* rings in the second umbilical cord from left to right. Subsequently, the areas of inflammation coalesce, and funisitis affects the entire umbilical cord.

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than that of the umbilical arteries.[40] This explains why the umbilical vein is the first vessel to show inflammatory changes, and the presence of arteritis is evidence of a more advanced fetal inflammatory response.[40] Indeed, the umbilical cord plasma concentrations of IL-6 (a cytokine used to define systemic inflammation) and the frequency of neonatal complications are higher in cases with umbilical arteritis than in those with only phlebitis.[41]

Systematic studies of the umbilical cord suggest that acute funisitis begins as multiple, discrete foci along the umbilical cord, which then merge as the inflammatory process progresses.[40] Figure 4 shows the topography of the inflammatory process in several umbilical cords that were sectioned serially at 1-mm intervals. The chemotactic gradient that attracted neutrophils from the lumen of the umbilical vessels into the Wharton's jelly is thought to be an elevated concentration of chemokines in the amniotic fluid. The severity of funisitis correlates with fetal plasma IL-6 concentrations (an indicator of the severity of the systemic fetal inflammatory response) and amniotic fluid IL-6; the latter reflects the intensity of the intraamniotic inflammatory response.[41]

## Histologic grading and staging of acute chorioamnionitis

Several grading and staging systems have been proposed to describe the severity of acute chorioamnionitis.[9,19,42-47]

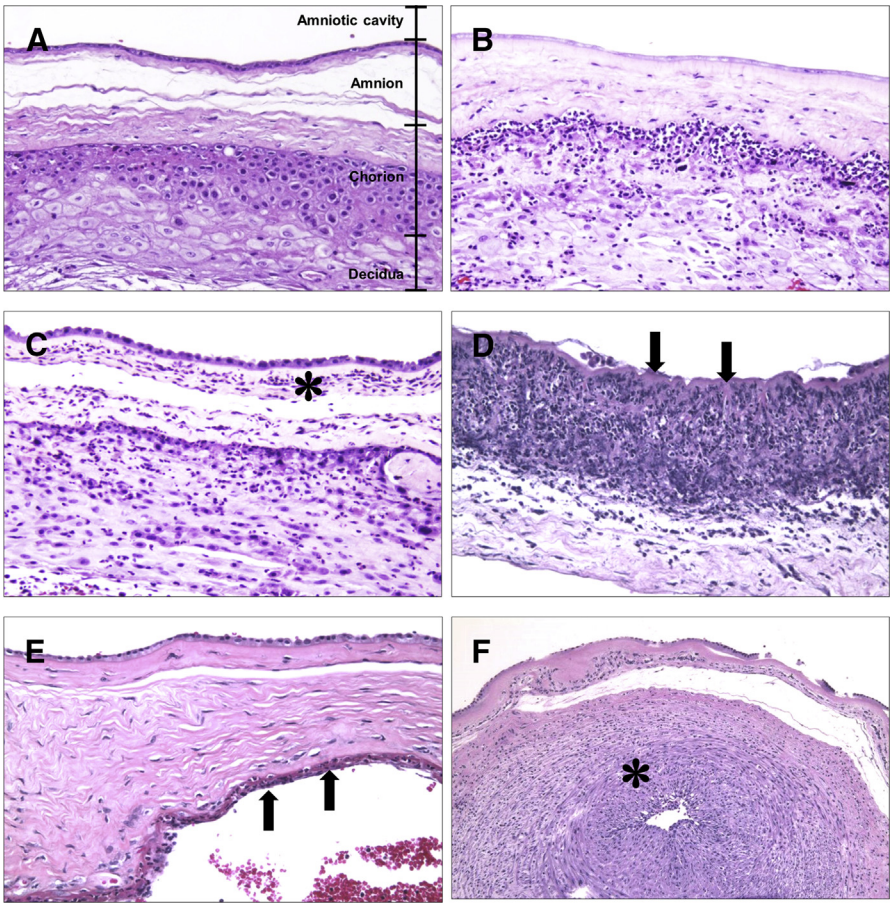
The most widely used system is that recommended by the Amniotic Fluid Infection Nosology Committee of the Perinatal Section of the Society for Pediatric Pathology and reported by Redline et al[9] in 2003. Although that article refers to the term *amniotic fluid infection syndrome*, it is now clear that these lesions do not always represent intraamniotic infection.

Redline et al[9] classified acute inflammatory lesions of the placenta into two categories: maternal inflammatory response and fetal inflammatory response. The term *stage* refers to the progression of the process based on the anatomical regions infiltrated by neutrophils; the term *grade* refers to the intensity of the acute inflammatory process at a particular site.[9] In the context of a maternal inflammatory response, a stage 1 lesion is characterized by the presence of neutrophils in the chorion or subchorionic space; stage 2 refers to neutrophilic infiltration of the chorionic connective tissue and/or amnion or the chorionic plate; and stage 3 is necrotizing chorioamnionitis with amnion epithelial necrosis.[9]

Grade 1 (mild to moderate) refers to individual or small clusters of maternal neutrophils that diffusely infiltrate the chorion laeve, chorionic plate, subchorionic fibrin, or amnion. Grade 2 (severe) consists of the presence of $\geq$3 chorionic microabscesses, which are defined as confluence of neutrophils measuring at least 10 $\times$ 20 cells.[9] Microabscesses typically are located between the chorion and decidua and/or under the chorionic plate.[9] Grade 2 is also applied in the presence of a continuous band of confluent neutrophils in the chorion of >10 cells in width that occupy more than one-half of the subchorionic fibrin or one revolution of the membrane roll. Other staging and grading systems have been used and subsequently modified.[19,42-47]

Staging and grading are also applicable to the fetal inflammatory response.[9] Staging (which refers to the location of neutrophil infiltration) is more important and reproducible than grading in the assessment of the severity of the inflammatory process.[48] For example, involvement of the amnion (amnionitis) is associated with more intense fetal and intraamniotic inflammation (assessed by the concentration of cytokines) than involvement of the chorion alone.[49] The rates of funisitis and positive amniotic fluid culture for microorganisms and the median umbilical cord plasma C-reactive protein, median amniotic fluid matrix metalloproteinase (MMP)-8 concentration, and amniotic fluid white blood cell count are higher when the inflammatory process involves amnion and chorion than when neutrophil infiltration is restricted to the chorion/decidua[49]

FIGURE 5
**Staging of acute chorioamnionitis**




Acute chorioamnionitis of the extraplacental chorioamniotic membranes: **A,** Normal chorioamniotic membranes shows the absence of neutrophils. **B,** Acute chorionitis is stage 1 acute inflammation of the chorioamniotic membranes, in which neutrophilic infiltration is limited to the chorion. **C,** Acute chorioamnionitis is stage 2 acute inflammation of the chorioamniotic membranes; neutrophilic migration into the amniotic connective tissue is shown (*asterisk*). **D,** Necrotizing chorioamnionitis is stage 3 acute inflammation of the chorioamniotic membranes, whose characteristic is the amnion epithelial necrosis (*arrows*). Acute inflammation of the chorionic plate: **E,** Acute subchorionitis, stage 1 acute inflammation shows neutrophils in the subchorionic fibrin in the chorionic plate (*arrows*). The area immediately below the arrows represents the intervillous space. **F,** Acute chorionic vasculitis (*asterisk*) is a stage 1 fetal inflammatory response. Acute inflammation of the chorioamniotic membranes (**A-E**) represents a maternal inflammatory response. Chorionic vasculitis is inflammation on the surface of the fetal vessels within the chorionic plate (Figure 1 presents the anatomical location).

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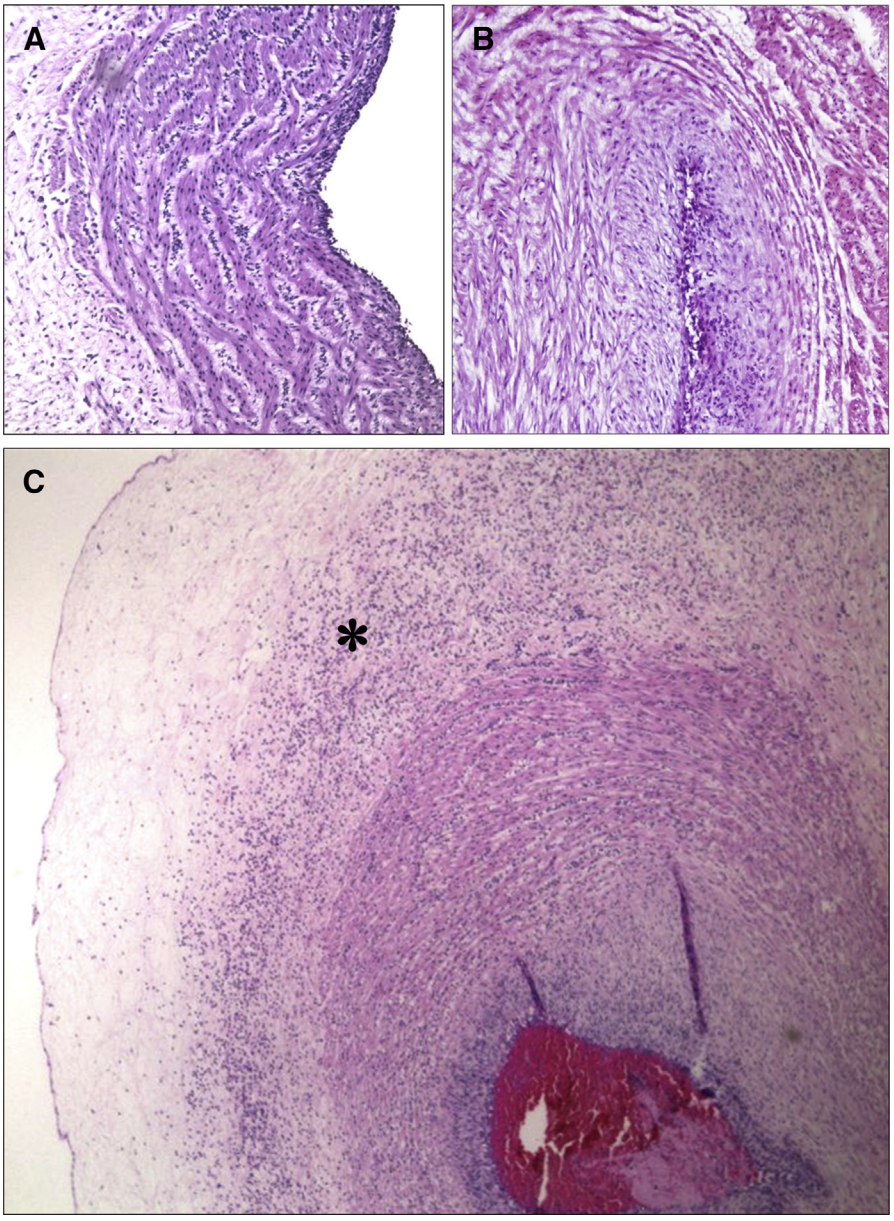
FIGURE 6
**Staging of acute funisitis**




**A,** Umbilical phlebitis shows amniotropic migration of fetal neutrophils into the muscle layer of the umbilical vein. Umbilical phlebitis represents stage 1 fetal inflammation. **B,** Umbilical arteritis is a stage 2 fetal inflammatory response. **C,** Necrotizing funisitis is considered stage 3 fetal inflammatory response. Its characteristic feature is concentric, perivascular distribution of degenerated neutrophils (*asterisk*). The presence of a thrombus should be considered to be a severe fetal inflammatory response.

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(Figures 5 and 6). Moreover, amniotic fluid MMP-8 concentration is correlated with the severity of acute chorioamnionitis (grading).[50]

The reproducibility of the grading and staging of maternal and fetal inflammation has been subject of a rigorous study by Redline et al[9]; 20 cases were reviewed by six pathologists who were asked to identify 12 inflammatory lesions. The kappa coefficient was used to measure agreement among observers. In general, the presence or absence of inflammation had a very high kappa value (0.93 for acute chorioamnionitis and 0.90 for acute chorioamnionitis/fetal inflammatory response). A kappa value between 0.81 and 1 is considered to represent almost perfect agreement. In contrast, the value of kappa was lower for the determination of grading and staging. The authors concluded that there is greater agreement among pathologists in identifying the presence or absence of inflammation, rather than in the assessment of grading and staging.[9]

## Pathways of microbial invasion of the amniotic cavity

Under normal conditions, the amniotic cavity is sterile for microorganisms with the use of cultivation[51] and molecular microbiologic techniques, based on the detection of the 16S ribosomal RNA (rRNA) gene (present in all bacteria, but not in mammalian cells). Four pathways have been proposed whereby microorganisms reach the amniotic cavity[52-56]: (1) ascending from the lower genital tract,[1,7,57,58] (2) hematogenous,[59-61] (3) accidental introduction at the time of amniocentesis, percutaneous umbilical cord blood sampling, fetoscopy, or another invasive procedure,[62-68] and (4) retrograde seeding from the fallopian tubes via the peritoneal cavity[57] However, there is limited evidence in support of the latter pathway.

Ascending microbial invasion from the lower genital tract appears to be the most frequent pathway for intraamniotic infection (Figures 7 and 8).[53] Although all pregnant women have microorganisms in the lower genital tract, most do not have intraamniotic infection. The mucus plug represents an anatomic and functional barrier to ascending infection during pregnancy.[69-75] In the nonpregnant state, the endometrial cavity is not sterile,[76-78] but the decidua is thought to be sterile during pregnancy.

A hematogenous pathway can operate during the course of blood-borne maternal infections.[59-61] Microorganisms such as *Listeria monocytogenes*,[79-81] *Treponema pallidum*, *Yersinia pestis*, cytomegalovirus, *Plasmodium species*, and others can gain access through the

maternal circulation to the intervillous space, from where they invade the villi and the fetal circulation.[53] Bacteria involved in periodontal disease may use this pathway to reach the amniotic cavity.[82-88]

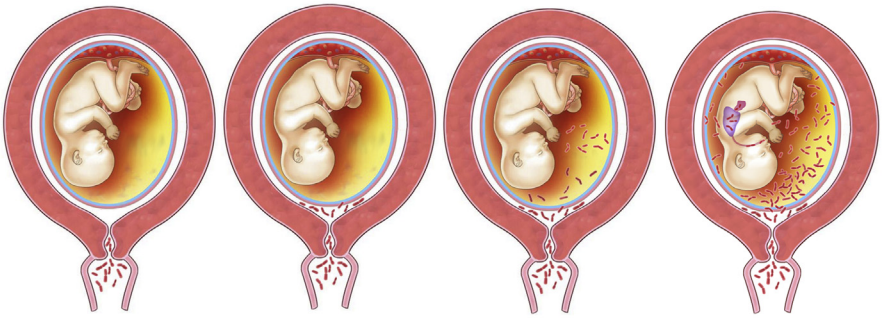
Intraamniotic infection has been documented in patients with preterm labor with intact membranes,[11,89-114] preterm prelabor rupture of the membranes,[13,115-130] cervical insufficiency,[131-135] asymptomatic short cervix,[14,136-138] idiopathic vaginal bleeding,[139] placenta previa,[140] and clinical chorioamnionitis at term.[15] Rupture of the membranes is not necessary for bacteria to reach the amniotic cavity; indeed, there is experimental evidence that bacteria can cross intact membranes.[141] Most of these infections are subclinical in nature; therefore, they occur in the absence of clinical chorioamnionitis.[90,142,143] Hence, these infections are undetected unless the amniotic fluid is analyzed. The most frequent microorganisms found in the amniotic cavity are genital mycoplasmas,[93,103,122,142,144-147] in particular, *Ureaplasma* species,[135,148-155] *Gardnerella vaginalis*,[15,90,127,156-158], and *Fusobacteria* species.[11,110,127] Fungi can also be found; women who become pregnant while using intrauterine contraceptive devices are at high risk for intraamniotic infection with *Candida albicans*.[159-168] Polymicrobial invasion of the amniotic cavity is present in approximately 30% of cases.[11,13,93,110,127,169] Table 2 contains information about the frequency of microbial invasion of the amniotic cavity in different obstetrical syndromes. Table 3 lists the microorganisms detected in the amniotic cavity of patients with preterm labor with intact membranes[110] and clinical chorioamnionitis at term.[15]

Microorganisms gaining access to the uterine cavity from the lower genital tract are first localized in the decidua of the supracervical region. Subsequent propagation and chorioamniotic passage of the microorganisms can lead to the establishment of microbial invasion of the amniotic cavity (Figures 7 and 8).[170,171] Although some investigators believe that there is a stage in which the bacteria are located diffusely in the choriodecidual layer, our studies, using FISH with a bacterial 16S rRNA probe, indicate that there is not extensive involvement of the chorion-decidua in cases with microbial invasion of the amniotic cavity.[172] Indeed, bacteria are primarily found in the amnion in cases of intraamniotic infection, which indicates that microbial invasion of the amniotic cavity is a prerequisite for substantial invasion of the amnion and chorion.[172] Specifically, bacteria are detected more frequently in the amniotic fluid than in the chorioamniotic membranes of patients with positive amniotic fluid culture (100% vs 33%; $P < .0001$; Figure 9).[172]

In the past, investigators have reported that the space between the chorioamniotic membranes could contain bacteria, even though such bacteria may not be detectable in the amniotic fluid.[4,173] The frequency with which this phenomenon occurs remains to be determined. Studies using a combination of cultivation and molecular microbiologic techniques to assess the frequency with which such a phenomenon occurs have not yet been conducted. This question is important for the understanding of the pathogenesis of intraamniotic infection. Experimental models in nonhuman primates have been generated by the inoculation of bacteria in either the decidua or amniotic cavity. Preterm labor occurs more frequently when bacteria are introduced into the amniotic cavity, rather than between the decidua and chorion.[171,174] Therefore, it seems that intraamniotic inoculation of bacteria more closely resembles the human disease.[171,174]

Microbial invasion of the amniotic cavity has traditionally been attributed to planktonic or free-floating bacteria. However, recent evidence suggests that amniotic fluid bacteria can form biofilms, defined as communities of sessile organisms that attach to a substratum or to each other.[175-182] The presence of biofilms can be suspected clinically when sludge is detected as particulate matter in the amniotic fluid with the use of ultrasound (Figure 10).[175-182] Bacteria in biofilms are embedded in a hydrated matrix of extracellular polymeric substances and exhibit an altered phenotype with respect to growth rate and gene transcription in comparison to planktonic (free-floating) cells.[183] Biofilms play a major role in human infections, such as periodontitis, otitis media, and endocarditis, and are important because

FIGURE 7
**Stages of ascending intraamniotic infection**




Stage I in the process of ascending infection corresponds to a change in the vaginal/cervical microbial flora or the presence of pathologic organisms in the cervix. Once microorganisms gain access to the amniotic cavity, they reside in the lower pole of the uterus between the membranes and the chorion (stage II). The microorganisms proceed through the amnion into the amniotic cavity that leads to an intraamniotic infection (stage III). The microorganisms may invade the fetus by different ports of entry (stage IV).

Modified from Figure 1 in Romero R.[53]

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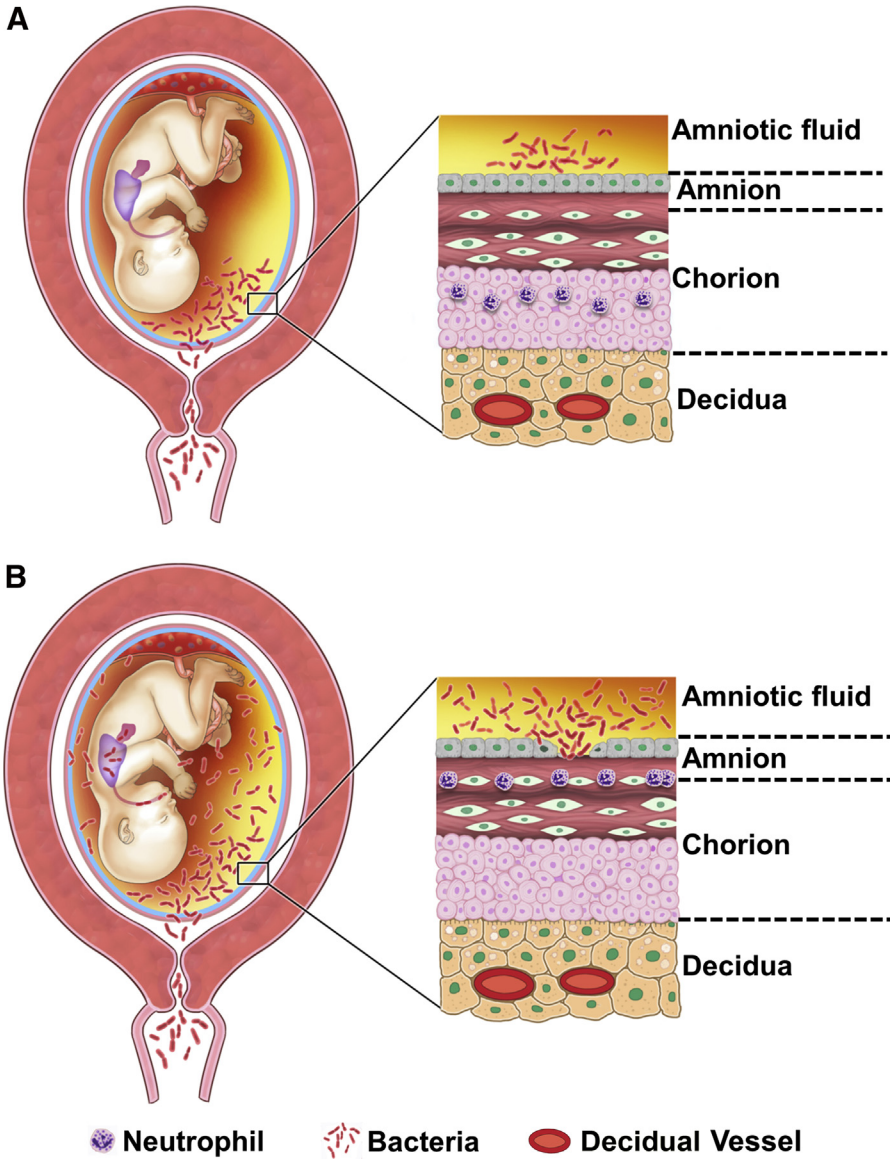
FIGURE 8
**Progression of intraamniotic infection**




**A,** Most cases of microbial invasion of the amniotic cavity are the result of ascending infection from the vagina and cervix. **B,** Extensive microbial invasion of the amniotic cavity can result in fetal infection (bacteria are located in the fetal lung) and damaged chorioamniotic membranes (ie, necrotizing chorioamnionitis). The destruction of the amnion epithelium is a cardinal feature of necrotizing chorioamnionitis.

Modified from Figure 5 in Kim MJ, et al.[172]

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bacteria organized in such structures are resistant to antibiotic treatment. The formation of biofilms in the amniotic cavity may explain the difficulty in the treatment of intraamniotic infection. Biofilms are also more common in infections associated with a device (eg, intrauterine contraceptive device, prosthetic valves, and catheters). Notably, eradication of intraamniotic infection diagnosed by amniocentesis in patients with preterm prelabor rupture of membranes (PROM)[184,185] and those with an asymptomatic short cervix[137] is possible with the administration of intravenous antibiotics to the mother. Success has been documented by demonstrating the absence of microorganisms at the time of a second amniocentesis.[137,184] We believe that the success of this treatment is due to the fact that the infections had been detected early, before biofilm formation and the onset of substantial intraamniotic inflammation. Once microbial invasion of the amniotic cavity leads to an intraamniotic cytokine storm clinically manifested by preterm labor, it is largely irreversible, and eradication of such infection has not been possible with antibiotic treatment.

## Inflammatory response to microbial invasion of the amniotic cavity

Microbial invasion of the amniotic cavity induces a robust local inflammatory response, and this is accompanied by a dramatic increase in the concentrations of proinflammatory cytokines such as IL-1,[31,32,34,106,186-192] tumor necrosis factor−α (TNF-α),[188-190,193-196] IL-6,[12,34,94,129,188,197-205] IL-8 (CXCL8),[26,187-189,196,199,200,202,206-211] and CXCL6,[212] as well as a cellular response (eg, increased neutrophil count). Table 4 describes the cytokines/chemokines involved in the inflammatory response to microbial invasion of the amniotic cavity.

Neutrophils express chemokine (C-X-C motif) receptor 2 (CXCR2), the receptor for both IL-8 and CXCL6, the potent chemokines for these leukocytes.[213-217] The primary cells and tissues responsible for an intraamniotic inflammatory response include fetal skin, cells that comprise the chorioamniotic membranes, and the umbilical cord. The amnion and chorion-decidua respond to bacterial products by increasing the expression of IL-1β[218-220] and TNF-α.[221,222] Amnion cells also synthesize IL-8.[223-225]

The temporal relationship between infection or the introduction of inflammatory stimuli (ie, endotoxin, IL-1, TNF-α, IL-6) in the amniotic cavity and the production of cytokines and prostaglandins has been studied extensively in nonhuman primate models,[174,190,226-237] sheep,[238-245] and other species (rabbits[246-252] and

mice[253-261]). Work from the laboratories of Gravett et al[226] and Novy et al,[232] in which maternal blood, amniotic fluid, and fetal blood have been sampled serially, provides unique information about the relationship between inflammation, prostaglandin production, and myometrial contractility.[226,234] Similar investigation has been conducted using sheep.[238-245] These studies have characterized the complex nature of the fetal immune response after exposure to live bacteria, bacterial products (endotoxin), or inflammatory cytokines (IL-1$\beta$).[237-245,262-265]

The gradient of chemokine concentrations that is established across the chorioamniotic membranes and the decidua is responsible for diffuse amniotropic infiltration of neutrophils into the chorioamniotic membranes.[53] A systematic proteomic analysis of the amniotic fluid in cases of intraamniotic infection and inflammation reveals dramatic changes in the protein composition and shows increased availability of matrix-degrading enzymes and other proteins involved in the mechanisms of membrane rupture (ie, neutrophil elastase) and host defense, such as lactoferrin (an antimicrobial protein), calgranulins, and alarmins such as heat shock protein and S100 proteins.[266,267]

The concentrations of cytokines, matrix-degrading enzymes, and other products released during the course of inflammation have been studied extensively to determine whether they have diagnostic and prognostic value in cases of suspected intraamniotic inflammation/infection. Thus far, amniotic fluid concentrations of MMP-8[268,269] and IL-6[101,111,124,198,270-272] appear to be the best predictors of pregnancy outcome and neonatal complications in patients with preterm labor and intact membranes[11,12,109,112,273,274] and preterm PROM[13,275] and in those who undergo genetic amniocentesis for standard clinical indications.[276-282] Originally tested as research methods, rapid analysis with point-of-care tests to identify intraamniotic inflammation with cytokines[113,130,205,283,284] and MMP-8 is now possible.[285-293]

Detection of microorganisms has traditionally relied on cultivation methods. However, novel approaches allow the identification of genes and species within 8 hours.[11] Increased amniotic fluid IL-6[195,294,295] and MMP-8[269,295] in patients who are at risk for preterm delivery is a risk factor for neonatal brain white matter lesions and the subsequent risk of cerebral palsy.

**TABLE 2**
**The frequency of microbial invasion of the amniotic cavity in obstetrical disorders[a]**

| Obstetrical disorders | Prevalence of microbial invasion of the amniotic cavity (%) |
|---|---|
| Spontaneous labor at term with intact membranes | 6.3-18.8[21,24,33,201] |
| Preterm labor with intact membranes | 8.7-34[11,89-104,106-114,327] |
| Preterm prelabor rupture of the membranes without labor | 17-57.7[13,97,98,115-130,327] |
| Clinical chorioamnionitis at term | 61[15] |
| Preterm prelabor rupture of the membranes in labor | 75[122] |
| Spontaneous rupture of membranes at term | 34.3[370] |
| Sonographic short cervix | 2.2-9[14,136-138] |
| Cervical insufficiency | 8-51.5[131-135] |
| Twin gestations with preterm labor and intact membranes | 11.9-35[371-373] |
| Meconium-stained amniotic fluid in preterm gestations | 33[374] |
| Meconium-stained amniotic fluid in term gestations | 19.6[375] |
| Placenta previa | 5.7[140] |
| Idiopathic vaginal bleeding | 14[139] |
| Pregnancy with intrauterine device | 45.9[168] |
| Preeclampsia | 1.6[376] |
| Small-for-gestational-age fetuses | 6[377] |
| Stillbirth | 2.3-13.3[378,379] |

[a] As determined by amniotic fluid studies that were obtained by transabdominal amniocentesis with the use of cultivation techniques.

*Kim. Acute inflammatory lesions of the placenta. Am J Obstet Gynecol 2015.*

## Pathogenesis: chemotactic signals in the amniotic cavity are responsible for acute chorioamnionitis and funisitis

Chemotactic stimuli are required for neutrophils to migrate into tissue (Figure 11).[215,216] Such stimuli are provided by neutrophil chemokines (eg, IL-8, also known as neutrophil-activating peptide, and CXCL6, a granulocyte chemotactic protein).[215,216,296] Intraamniotic inflammation due to microorganisms or "danger signals" can result in the production of the following chemokines: IL-8[26,187-189,196,199,200,202,206-210], macrophage inhibitory cytokine,[297,298] MCP,[27,299-302] MCP-2, MCP-3,[303] MIP-1$\alpha$.[29,196,302,304] CXCL6,[212] CXCL10,[281] CXCL13,[305] epithelial-derived neutrophil-activating peptide 78,[306] regulated on activation, normal T cell expressed and secreted (RANTES),[307] and GRO-$\alpha$.[28,208] Elevated amniotic fluid chemokines establish a chemotactic gradient that favors the migration of neutrophils. In the absence of microorganisms, danger signals released by cells under stress

TABLE 3
**Microorganisms in the amniotic cavity**[a]

| Patients with spontaneous preterm labor with intact membranes[110] | Patients with clinical chorioamnionitis at term[15] |
|---|---|
| *Fusobacterium nucleatum* | *Ureaplasma* species |
| *Sneathia sanguinegens* | *Gardnerella vaginalis* |
| *Ureaplasma* species | *Mycoplasma hominis* |
| *Streptococcus mitis* | *Streptococcus agalactiae* |
| *Gardnerella vaginalis* | *Lactobacillus* species |
| *Peptostreptococcus* species | *Bacteroides* species |
| *Leptotrichia amnionii* | *Acinetobacter* species |
| *Mycoplasma hominis* | *Sneathia* |
| *Streptococcus agalactiae* | *Streptococcus viridans* |
| *Lactobacillus* species | *Porphyromonas* species |
| *Bacillus* species | *Veillonella* species |
| Coagulase-negative *Staphylococcus* species | *Peptostreptococcus* species |
| *Prevotella* species | *Escherichia coli* |
| Others: uncultivated *Bacteroidetes, Delftia acidovorans, Neisseria cinerea* | *Pseudomonas aeruginosa* |
| | *Staphylococcus aureus* |
| | *Eubacterium* species |
| | Gram negative bacilli |
| | *Enterococcus* species |
| | Others: *Fusobacterium* species, *Candida* species, *Abiotrophia defective, Micrococcus luteus, Staphylococcus epidermidis, Firmicute, Propionibacterium acnes* |

[a] Detected with the use of cultivation and molecular microbiologic techniques in the amniotic fluid of patients with spontaneous preterm labor with intact membranes and patients with clinical chorioamnionitis at term.

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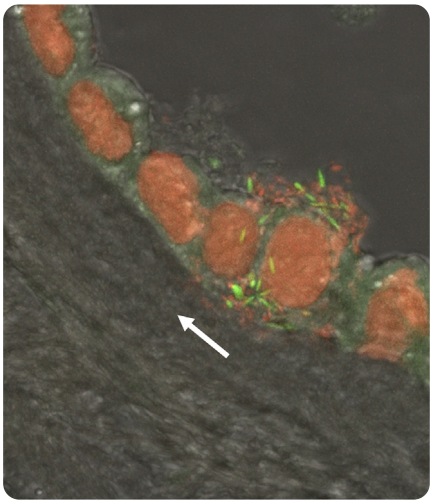
FIGURE 9
**Bacterial invasion of amniotic epithelial cells demonstrated by fluorescent staining**



Live bacteria were stained with SYTO 9 (*green fluorescence*); dead bacteria were stained with propidium iodide (*red fluorescence*). Note the lack of bacteria in the chorioamniotic connective tissue, which indicates bacterial propagation from the amniotic cavity (*white arrow*).

Modified from Figure 3C in Kim MJ, et al.[172]

*Kim. Acute inflammatory lesions of the placenta. Am J Obstet Gynecol 2015.*

conditions or cell death can induce intraamniotic inflammation ("sterile inflammation").[308-319] The diagnosis of this condition is one of exclusion and requires examination of the amniotic fluid with both cultivation and molecular microbiologic techniques.[11-15]

## Acute chorioamnionitis should not be equated with intraamniotic infection

Acute inflammatory lesions of the placenta have been considered to reflect the presence of amniotic fluid infection.[1-10,149,320-322] In 1987, Dong et al[323] reported that acute chorioamnionitis was present in 97% of patients (32/33) with intraamniotic infection, defined as the presence of microorganisms detected using cultivation techniques. However, the amniotic fluid samples in that study were obtained by transcervical collection.[323] Interestingly, acute chorioamnionitis was found in 37% of patients (18/49) with negative amniotic fluid cultures.[323]

The most rigorous evidence that intraamniotic infection is associated with acute chorioamnionitis is derived from studies in which a transabdominal amniocentesis was performed in patients with preterm labor and intact membranes, and the placenta was examined within 48 hours of the procedure.[7] Placentas with acute chorioamnionitis and acute funisitis were from mothers who had intraamniotic infection that had been proven by culture in 71.1% and 78.7% of cases, respectively.[7] The prevalence of microbial invasion of the amniotic cavity was 38%. The negative predictive values of acute chorioamnionitis and funisitis for intraamniotic infection were 87% and 82%, respectively.[7]

Recently, we reported that *sterile inflammation* is more frequent than intraamniotic infection (microbial-associated intraamniotic inflammation) in patients with preterm labor with intact membranes,[12] preterm PROM,[13] and an asymptomatic short cervix.[14] Interestingly, sterile intraamniotic inflammation is associated with acute chorioamnionitis (40-60% of cases).[11-15] Importantly, acute inflammatory lesions of the placenta are present in a small subset of patients without intraamniotic

inflammation in the context of preterm labor,[11,13] preterm PROM,[13] short cervix,[14] and clinical chorioamnionitis.[15] Potential explanations are (1) the inflammation of chorioamniotic membranes is a nonspecific mechanism of host defense against "danger signals" of nonmicrobial origin, (2) extraamniotic infection, which is probably rare, and (3) nonviable microorganisms that may release chemotactic factors that lead to placental inflammation.[7] The latter could be due to microorganisms which invaded the amniotic cavity and then cleared through the immune system.

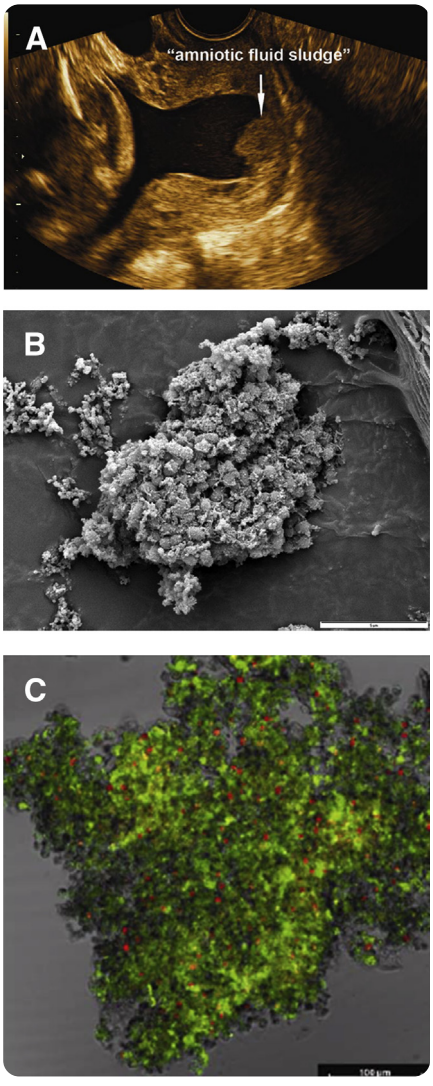
The observation that acute chorioamnionitis can be present without demonstrable intraamniotic infection has recently gained support.[11-15,324] Roberts et al[324] reported, using both cultivation and molecular microbiologic techniques, that only 4% of patients with acute chorioamnionitis at term have microorganisms in the placenta. The characterization of any biologic fluid as "sterile" is dependent on the sensitivity of the assays used to detect microorganisms. Cultivation can be very sensitive, and even one microorganism can grow into a colony under optimal conditions; however, such conditions are rarely present in clinical laboratories. Molecular microbiologic techniques are considered more sensitive; yet, sufficient microbial DNA must be present for this method to provide a positive result. PCR assays with specific primers for a microorganism are considered superior to broad range PCR assays that are based on conserved regions of the bacterial genome (eg, 16S rRNA gene). The use of deep sequencing can change what is known about the microbiologic landscape of biologic fluids. Extreme caution must be used when interpreting the results of sequencing studies, because contamination during metagenomics studies can occur.

## The host response to microbial invasion of the amniotic cavity is stronger in preterm than in term gestations

The frequency of microbial invasion of the amniotic cavity is similar in patients with spontaneous labor at term and those with preterm labor and intact membranes who subsequently deliver a preterm neonate (17% vs 22%, respectively).[24,93] Yet, preterm neonates born to mothers with microbial invasion of the amniotic cavity have a higher frequency of neonatal sepsis, a systemic inflammatory response (defined as an elevated umbilical cord IL-6 concentration), and funisitis than those born to mothers at term with microbial invasion of the amniotic cavity. Why? Microbial invasion of the amniotic cavity in women in spontaneous labor at term is of shorter duration and can occur after the initiation of parturition.[201] For example, bacteria can be introduced when the chorioamniotic membranes are exposed to the vaginal microbiota during the course of digital examinations performed during labor to determine cervical dilation and effacement. Such microbial invasion typically has a low inoculum size that elicits a mild intraamniotic inflammatory response and rarely leads to fetal microbial invasion (hence, the low frequency of funisitis and neonatal sepsis).

On the other hand, in preterm labor with intact membranes or preterm PROM, microbial invasion is established before the initiation of preterm labor. Such infections have a higher microbial burden than those that are observed in most women in spontaneous labor at term, have probably lasted longer, and therefore result in a more intense intraamniotic inflammatory response.[201] Given the longer duration of infection, the likelihood of a fetal attack is higher; thus, the rate of congenital neonatal sepsis is greater in preterm neonates than in term neonates (2.27-5.14/1000 in preterm neonates vs 0.04-0.89/1000 term neonates).[325]

FIGURE 10
**Microbial biofilms in the amniotic cavity**




**A,** Two-dimensional transvaginal ultrasound image shows the presence of "amniotic fluid sludge." **B,** Scanning electron micrograph of a floc of "amniotic fluid sludge" shows the bacterial cells and the exopolymeric matrix material that constitute a biofilm. In the center of the image, cocci are resolved among a fibrous mass of matrix material. **C,** Confocal laser scanning microscopy displays bacteria (*red dots*), matrix material (*green*), and some unstained material that is likely to represent host components trapped by the biofilm. The *bar* represents 100 microns. Bacteria (*red dots*) are stained with the EUB338-Cy3 probe, which reacts with bacterial 16S ribosomal RNA. The matrix material has been stained with wheat germ agglutinin, which reacts with the N-acetylglucosamine of the component of the matrix material that forms the structural framework of the biofilm.

Modified from Figures 1, 3, and 4 in Romero R, et al.[179]

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TABLE 4
**Cytokines implicated in the pathogenesis of intraamniotic inflammation/infection**

| Variable | Function |
|---|---|
| Pro- and antiinflammatory cytokines | |
| IL-1$\alpha$ (IL1F1)[32] | Alarmin (endogenous molecules that signal tissue and cell damage) |
| | Proinflammatory effects by inducing production of cytokines and chemokines |
| | Mediates neutrophil recruitment |
| IL-1$\beta$ (IL1F2)[32] | Proinflammatory cytokine and a major mediator of the inflammatory response |
| IL-6[94,380] | Key mediator of the acute phase response to infection and tissue injury |
| | Activates T cells and natural killer cells |
| | Stimulates proliferation and immunoglobulin production by B cells |
| Tumor necrosis factor-$\alpha$[381] | Proinflammatory cytokine and a major mediator of sepsis |
| IL-4[382] | Inhibits production of IL-1$\beta$ |
| | Induces differentiation of helper T cells |
| | Stimulates immunoglobulin G and E production |
| IL-10[383] | Inhibits the production of proinflammatory cytokines (cytokine inhibitory factor) |
| | Down-regulates T-cell functions |
| | Potent suppressor of the effector functions of macrophages and natural killer cells |
| Chemokines | |
| IL-8 (neutrophil-activating peptide, CXCL8)[26] | Recruitment and activation of acute inflammatory cells, primarily neutrophils |
| | Promotes angiogenesis |
| CXCL6 (granulocyte chemotactic protein-2)[212] | Potent proinflammatory chemokine |
| | Neutrophil activator |
| CXCL10 (Interferon-gamma-inducible protein-10)[281,283] | T-cell chemotactic cytokine |
| | Recruits and potentiates helper T-cell responses and pathogenesis of allograft rejection |
| | Proinflammatory and antiangiogenic properties |
| CXCL13 (B-cell—attracting chemokine-1)[305] | Induces migration of B and T lymphocytes to areas of infection and inflammation |
| CCL3 (MIP-1$\alpha$)[29] | Chemotactic cytokine, activates human granulocytes (neutrophils, eosinophils and basophils) in response to inflammation and infection |
| CCL4 (MIP-1$\beta$)[196] | Chemotactic cytokine, activates human granulocytes (neutrophils, eosinophils and basophils) in response to inflammation and infection |
| CCL20 (MIP-3$\alpha$)[384] | Chemotactic activity for immature dendritic cells, effector or memory CD4(+) T lymphocytes, and B lymphocytes |
| Macrophage inhibitory cytokine[298] | Regulates the adaptive immune response and induces cell proliferation and angiogenesis |
| | Inhibits the migration of macrophages and stimulates tumor necrosis factor-$\alpha$ and nitric oxide from macrophages and IL-2 production |
| MCP-1 (CCL2)[300] | Recruits monocytes/macrophages into sites of inflammation |
| | Stimulates the respiratory burst required for macrophage activation |
| MCP-2 (CCL8)[303] | Role in the inflammatory response |
| | Activates immune cells (including mast cells, eosinophils and basophils, monocytes, T cells, and natural killer cells) |

*Kim. Acute inflammatory lesions of the placenta. Am J Obstet Gynecol 2015.* *(continued)*

TABLE 4
**Cytokines implicated in the pathogenesis of intraamniotic inflammation/infection** *(continued)*

| Variable | Function |
|---|---|
| MCP-3 (CCL7)[303] | Monocyte chemoattractant |
| | Regulates macrophage function |
| Epithelial-derived neutrophil-activating peptide-78 (CXCL5)[306] | Potent neutrophil chemoattractant and activator |
| | Ligand for CXCR2 (IL-8 receptor; chemokine receptor that is activated by IL-8) |
| Growth-regulated oncogene-$\alpha$ (CXCL1)[28] | Recruits and activates neutrophils, lymphocytes, and monocytes in host defense |
| | Role in wound healing, growth regulation, angiogenesis, tumorigenesis, and apoptosis |
| Regulated on activation, normal T cell expressed and secreted [307] | Chemoattractant of monocytes, lymphocytes, basophils, and eosinophils |
| | Regulates the inflammatory response and recruitment of macrophages to the implantation site in early pregnancy |
| | Regulates the host response to intrauterine infection |

*CCL*, chemokine (C-C motif) ligand; *CXCL*, chemokine (C-X-C motif) ligand; *IL*, interleukin; *MCP*, monocyte chemotactic protein; *MIP*, macrophage inflammatory protein.

*Kim. Acute inflammatory lesions of the placenta. Am J Obstet Gynecol 2015.*

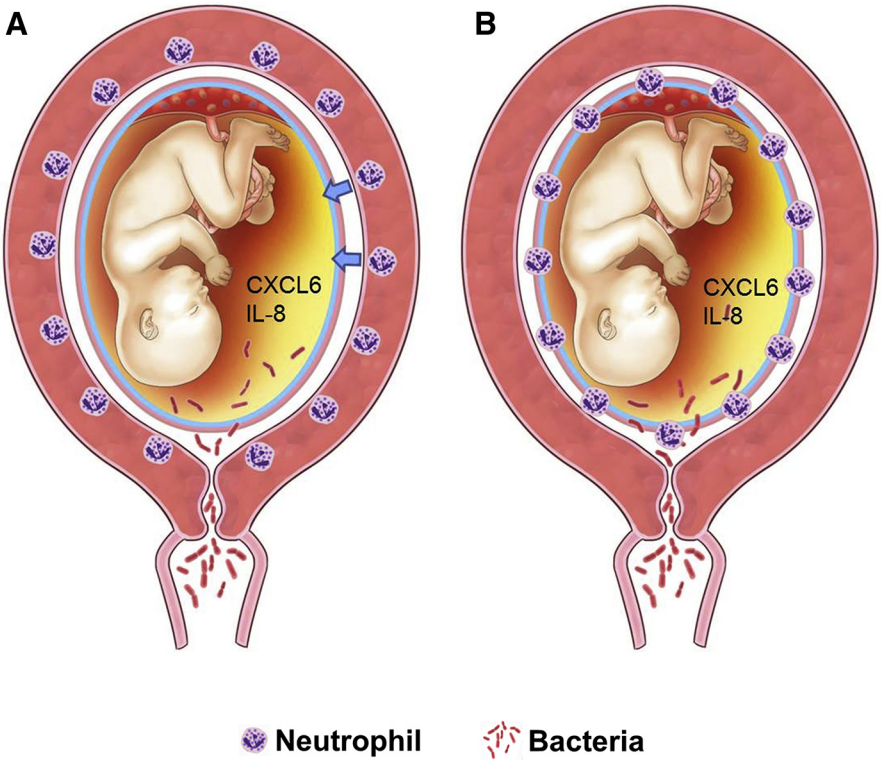
## The fetal inflammatory response syndrome

Microbial invasion of the amniotic cavity can progress to fetal invasion. The ports of entry for bacteria into the fetus include the respiratory tract, gastrointestinal tract, skin, and ear. (Amniotic fluid fills the external auditory canal, and bacteria can invade the tympanic membrane and middle ear). Similarly, depending on the gestational age, microorganisms may gain access to the conjunctiva.

Once microorganisms gain access to the fetal mucosa, they are recognized by pattern recognition receptors such as Toll-like receptors, and ligation of such receptors can induce the deactivation of transcription factors such as NF$\kappa$B and elicit a localized (and subsequently systemic) inflammatory response.[326] For example, fetuses who are exposed to bacteria can have severe dermatitis or pneumonitis. Subsequently, microorganisms that reach the fetal circulation could lead to a systemic inflammatory response.

The frequency with which microorganisms invade the human fetus is difficult to ascertain; however, studies in which amniocentesis and cordocentesis have been performed in patients with

FIGURE 11
**Chemotactic stimuli induce neutrophils to migrate into the fetal membranes**




**A,** An increase in the amniotic fluid concentrations of chemokines such as CXCL6 and interleukin-8 induces neutrophils to migrate toward the amnion (*arrows*). **B,** As a consequence, maternal neutrophils infiltrate the chorioamniotic membranes from the decidual vessels.

*IL-8*, interleukin-8; *CXCL6*, chemokine (C-X-C motif) ligand-6.

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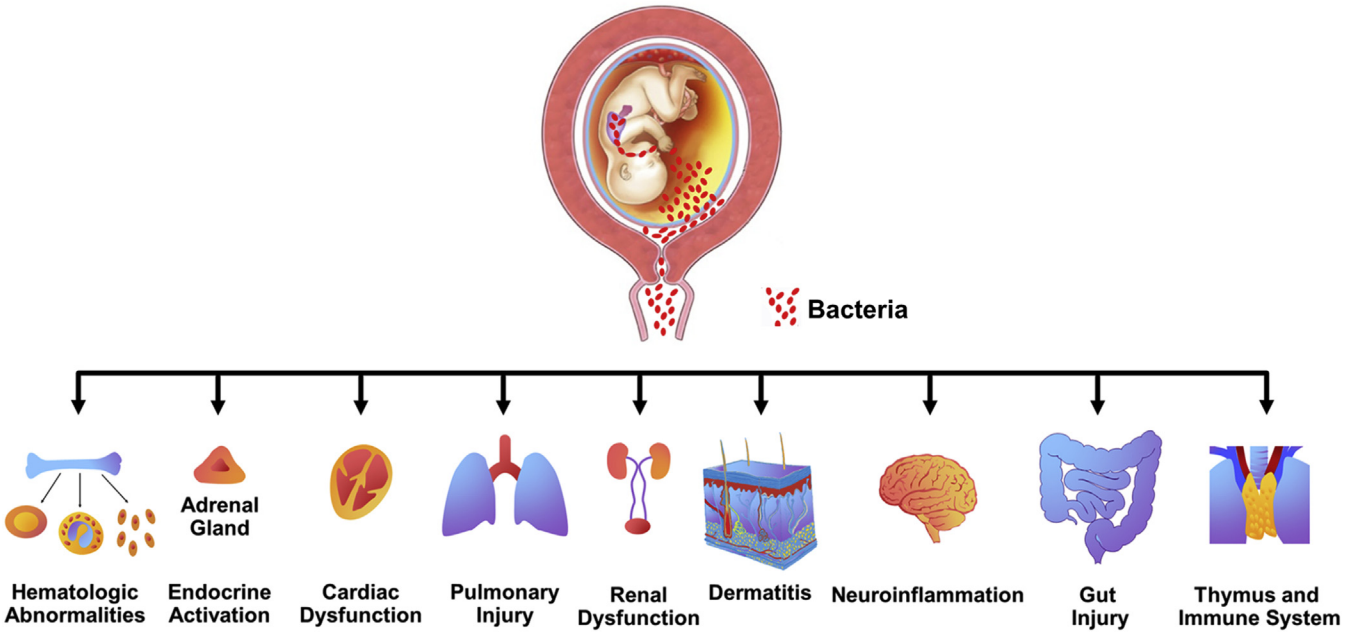
FIGURE 12
**Fetal target organs during fetal inflammatory response syndrome, type 1**




Modified from Figure 2 in Gotsch F, et al.[351]

*Kim. Acute inflammatory lesions of the placenta. Am J Obstet Gynecol 2015.*

preterm PROM indicate that 30% of patients with microbial invasion of the amniotic cavity have positive fetal blood cultures for microorganisms (ie, bacteremia).[327,328] Similar findings have been reported when cultures for genital mycoplasmas have been performed in umbilical cord blood at the time of birth.[144,329] Therefore, the frequency of congenital microbial invasion of the fetus is likely to be higher than that reported in the pediatric literature: the reasons for this are multiple (eg, bacteremia may not be continuous in the neonatal period; the inoculum size may be small and lead to a high rate of negative blood cultures; and the lack of detection of the most common microorganisms, genital mycoplasmas, may reflect that cultures for these organisms require special media, and such cultures are not performed routinely in neonatal intensive care units).[330-332]

We have defined FIRS as an elevated fetal plasma concentration of IL-6.[16,327,333-343] This cytokine is a major mediator of the acute phase response, and its concentration can be easily determined with the use of immunoassays. It is noteworthy that the systemic inflammatory response syndrome (SIRS, in adults) was defined originally with clinical criteria such as fever, tachycardia, respiratory rate, and white blood cell count.[344-346] However, this definition cannot be used in the human fetus because the vital signs (with the exception of heart rate) cannot be determined readily before birth or during the intrapartum period.[347] Our definition of FIRS was based on the concentration of fetal plasma IL-6 associated with adverse outcome[327] and was introduced in 1997.[348] Subsequently, in 2001, the American College of Chest Physicians and the Society of Critical Care Medicine noted that an elevated plasma concentration of IL-6 was associated with the likelihood of SIRS and proposed that the concentrations of this cytokine may be useful in its diagnosis.[349]

Despite the similarities between FIRS and SIRS, the unique circumstances of the patient (fetus)[330] and its environment (uterus) pose challenges that are sui generis for the diagnosis, management, and treatment of FIRS.[56,143,350,351] Importantly, FIRS and SIRS can be caused by nonmicrobial-related insults. SIRS can occur in cases of sterile inflammation (eg, pancreatitis or burns).[346,352] Since the original report of FIRS, we have noted that some cases of this syndrome are observed without demonstrable microbial invasion of the amniotic cavity.[11-13] The precise nature of the danger signals in sterile intraamniotic inflammation and corresponding cases of FIRS has not been elucidated; yet, it is possible that this may result from insults that trigger cell death (eg, necrosis, pyroptosis).[308,310,311,314,316,318]

The presence of FIRS was originally described in fetuses with preterm labor and preterm PROM[327] and was associated with three major consequences: (1) a shorter interval-to-delivery,[327] (2) higher neonatal morbidity after adjustment for gestational age at birth,[327] and (3) multiorgan involvement[351] that included the hematopoietic system,[336,338,339,353] immune system,[336,353-356] thymus,[357-361] heart,[362] adrenal glands (eg, alteration in

cortisol),[363] skin,[335] lung,[188,333] brain,[195,294,364-366] kidney,[367] and gut[46,368,369] (Figure 12). Although these observations were originally made in humans, subsequent experimental studies in nonhuman primates and sheep have demonstrated the involvement of multiple organ systems when the fetus is exposed to inflammatory stimuli.[242] A full description of fetal immune response to chorioamnionitis/intraamniotic infection in the animal model is available in a review by Kallapur et al.[242]

## Conclusion

Acute chorioamnionitis and acute funisitis are acute inflammatory lesions with important short- and long-term clinical significance. Substantial progress has been made in the understanding of the mechanisms responsible for maternal and fetal inflammation in the context of infection. Determining the causes of sterile intraamniotic inflammation represents an important clinical and scientific challenge. ■

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