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Chorioamnionitis: from pathogenesis to treatment

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Abstract

Chorioamnionitis refers to inflammation of the amniochorionic membrane, and is a significant cause of maternal and neonatal morbidity. Chorioamnionitis most often occurs as a result of ascending infection, and is commonly associated with premature rupture of the membranes. Chorioamnionitis is generally the result of a polymicrobial infection, with *Ureaplasma urealyticum*, *Mycoplasma hominis* and Gram-negative anaerobes being frequent causative organisms. The mainstay of treatment includes antimicrobial agents, antipyretics, expedition of delivery and supportive care. Further research is required to identify mechanistic pathways and early biomarkers that accurately predict women at higher risk of adverse maternal and neonatal outcomes, and that can thus lead to the development of additional treatment and prevention strategies.

Keywords: Antibiotic therapy, chorioamnionitis, intra-amniotic infection, PPROM, prevention

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Introduction

Chorioamnionitis (or intra-amniotic infection) refers to inflammation of the amniochorionic membrane (both chorion and amnion). It is estimated to be present in approximately 2–4% of term pregnancies [1], and in approximately 40–70% of women who deliver prematurely [2,3]. Chorioamnionitis can be defined both clinically, on the basis of maternal symptoms including fever, abdominal pain, abnormal vaginal discharge and leukocytosis [4], and histologically, with evidence of inflammation and necrosis throughout the chorionic plate and amnion [5]. Chorioamnionitis is associated with significant maternal and neonatal morbidity and mortality. Neonatal morbidities include an increased risk of neonatal sepsis and pneumonia [6]. Furthermore, chorioamnionitis may result in a fetal inflammatory response syndrome, which carries with it increased risks of periventricular leukomalacia, cerebral palsy [7] and chronic lung disease [8]. The earlier the degree of prematurity, the higher the likelihood of detecting histological chorioamnionitis. One study found that, of those cases delivering at 21–24 weeks, 67% demonstrate evidence of histological infection and inflammation, as compared with 22% of those delivering at 33–36 weeks [9]. In addition to these fetal and neonatal complications, chorioamnionitis can pose significant maternal risks. These include postpartum haemorrhage, uterine atony, increased risk of caesarean section, and rarer complications such as septic shock, adult respiratory distress syndrome and coagulopathies [10]. Caesarean section performed in the presence of intra-amniotic infection is associated with an increased risk of maternal blood transfusion, septic pelvic thrombophlebitis, pelvic abscess formation [11] and surgical site infections [12]. These complications result not only in significant maternal morbidity, but also in increased healthcare costs.

Aetiology of Chorioamnionitis

Chorioamnionitis occurs most often as a result of ascending bacteria from the vagina and cervix, and is most commonly seen as a secondary complication of prolonged rupture of the membranes [13]. Less common modes of transmission include haematogenous spread or transmission following an invasive procedure (i.e. amniocentesis, chorionic villous sampling or other fetal procedure). Various bacterial, viral and, rarely, fungal agents have been linked to the underlying pathogenesis of chorioamnionitis and preterm birth (PTB). Some of these commonly identified pathogens include *Ureaplasma urealyticum*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Mycoplasma hominis*, group B streptococcus and *Trichomonas vaginalis* [14,15]. Additional bacteria include Gram-negative anaerobes, including *Gardnerella vaginalis* and *Bacteroides* spp. [16].

Cultured specimens from patients with clinical chorioamnionitis most often reveal a polymicrobial infection, with the majority of women having at least two detectable pathogens. The frequency of isolation of certain pathogens in chorioamnionitis varies with the study and the type of tissue analysed. The most frequent isolates from placentas of preterm infants were *U. urealyticum* (47%) and *G. vaginalis* (26%) [3]. Similar microbiological isolates were detected in the amniotic fluid of women with intra-amniotic infection, with the most common organisms detected being *U. urealyticum* (47%), any Gram-negative anaerobe (38.4%), *M. hominis* (30.4%), *Bacteroides bivius* (29.5%) and *G. vaginalis* (24.5%) [16].

Viruses may also play a role in chorioamnionitis. Multiple viruses, including cytomegalovirus, adenovirus, enterovirus, respiratory syncytial virus and Epstein–Barr virus, have been isolated from amniotic fluid [17]. Recently, investigators demonstrated that placental adenovirus infection was strongly associated with histological chorioamnionitis (75% vs. 36%; p 0.026) and PTB (41% vs. 21%; OR 2.6; 95% CI 1.4–5.1; p <0.002) [18]. Although these viruses have been isolated and implicated in cases of chorioamnionitis, supportive evidence for viruses, including Epstein–Barr virus and others, actually causing chorioamnionitis is very limited.

Fungal organisms, including several species of *Candida* (*Candida albicans*, *Candida tropicalis* and *Candida glabrata*), have also been associated with chorioamnionitis [19–21]. These infections have been reported in women with *in vitro* fertilization pregnancies, in those with retained intrauterine contraceptive devices, following amniocentesis, and in those with prolonged rupture of membranes [19,22,23]. Only 0.8% of candidal vaginal infections actually ascend into the uterus, and even fewer result in acute chorioamnionitis [20]. However, the complications of intra-amniotic fungal infection can be severe, with a 75% risk of prematurity being associated with candidal funisitis [20]. Also, there are increased risks of mortality in immature/low-birthweight (<1500 g) infants with congenital systemic candidiasis [24].

Finally, there have been case reports of methicillin-resistant *Staphylococcus aureus* causing chorioamnionitis, but there are no reports at the time of publication of chorioamnionitis associated with vancomycin-resistant *Enterococcus*. Methicillin-resistant *S. aureus* and possibly vancomycin-resistant *Enterococcus* infection should be considered in women with clinical chorioamnionitis refractory to treatment, as well as in those with recurrent or prolonged admission to hospital or who themselves are healthcare workers [25,26].

Organisms such as *Mycoplasma* are typically low-virulence organisms, which may explain why women with histological chorioamnionitis often have no clinical symptoms. Despite multiple reports documenting the positive culture of bacteria and/or viruses from women with chorioamnionitis, the presence of bacteria and their products alone is not sufficient to induce chorioamnionitis. In addition to the presence of these bacteria/viruses, the elicited host immune response plays an integral role in determining outcomes, including clinical chorioamnionitis, PTB and premature preterm rupture of the membranes (PPROM) [27,28]. Research is ongoing, including projects such as the Human Microbiome Project. This group works to further characterize the microbial communities found in the female genital tract, both in normal pregnancy and in pathological conditions such as chorioamnionitis (31st Annual Meeting of the Society for Maternal Fetal Medicine, Abstract 73) [29].

Risk factors for Chorioamnionitis

Apart from colonization with bacteria and viruses, there are several risk factors for the development of chorioamnionitis. As discussed above, prematurity and PPROM are commonly associated with chorioamnionitis. At term, risk factors include long duration of labour and rupture of membranes, and nulliparity [30]. Furthermore, women with pre-labour rupture of membranes at term who receive multiple digital vaginal examinations, have a prolonged labour or have meconium-stained liquor are at higher risk of developing chorioamnionitis [31].

Diagnosis

Chorioamnionitis can be diagnosed with the use of histological or clinical criteria. The clinical diagnosis is based on signs