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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.

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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

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and symptoms of local or systemic infection. A common definition includes maternal pyrexia (fever >37.5–38°C) and one of the following: abdominal pain, uterine tenderness, foul vaginal discharge, maternal tachycardia (>100 beats/min), fetal tachycardia (persistent elevation of fetal heart rate >160 - beats/min) and an elevated maternal white blood cell count (>15 000 cells/mm^3) [4,32,33]. The cut-off for maternal pyrexia varies across several studies, but more recent literature generally quotes a value for definition purposes of >38.0°C, to exclude the many women with a low-grade fever during labour unrelated to an infectious process.

Chorioamnionitis can occur histologically, and is staged on the basis of specific criteria, with increasing neutrophil infiltration and the development of necrosis, amnion basement membrane thickening and chorionic microabscesses being seen with increasing disease severity [5] (Fig. 1). In addition, the fetal inflammatory response may progress from chorionic/umbilical vasculitis (neutrophil infiltration in the chorionic or umbilical vessels) to necrotizing funisitis (inflammation of the connective tissue of the umbilical cord) [5]. The clinical diagnosis of chorioamnionitis, however, is not always confirmed by histological or microbiological studies. In one study of 139 pregnancies with clinical findings of chorioamnionitis, histological examination of the placenta did not support the clinical diagnosis in approximately one-third of cases [34].

Chorioamnionitis, as defined by positive amniotic fluid cultures, is found in 36% of women with PPROM [35]. Although amniocentesis with culture of the amniotic fluid is ideal for isolating bacteria, and is the reference standard for the purposes of diagnosis, this test is associated with a delay of at least 48 h for cultures, with no evidence of predictive value for potential maternal and neonatal outcomes. There is also a lack of good-quality trials to demonstrate that this approach reduces either maternal or neonatal morbidity. One study investigated the use of amniocentesis, placental swabs and neonatal skin swabs in the subsequent management of chorioamnionitis following delivery. There was a strong association between positive amniotic cavity culture results and clinical early-onset sepsis; however, there remains insufficient evidence to justify the routine performance or recommendation of amniocentesis for the purposes of diagnosis [35,36].

The evidence supporting the use of blood cultures for the diagnosis of chorioamnionitis is also limited. It appears that the routine use of maternal blood cultures rarely provides information that justifies a change in clinical management when patients are treated in accordance with a specific antibiotic protocol [37]. Furthermore, there is no good-quality evidence to show the benefit of the use of high vaginal swabs in the diagnosis and management of chorioamnionitis. In fact, the Royal College of Obstetricians and Gynaecologists recommends that, in the management of PPROM, women should be observed for signs of clinical chorioamnionitis, and weekly high vaginal swabs should not be performed [35].

Several laboratory assessments have been investigated for their potential usefulness in the early prediction and diagnosis of chorioamnionitis. A low vaginal 'pool' amniotic fluid glucose measurement (<5 mg/dL) was shown to be a predictive but not sensitive marker for infection in women with PPROM [38]. Similarly, several potential biomarkers of early chorioamnionitis have been identified, including interleukin-6, interleukin-8, C-reactive protein, matrix metalloproteinase-8, ferritin and placental alkaline phosphatase [4]. The reliability

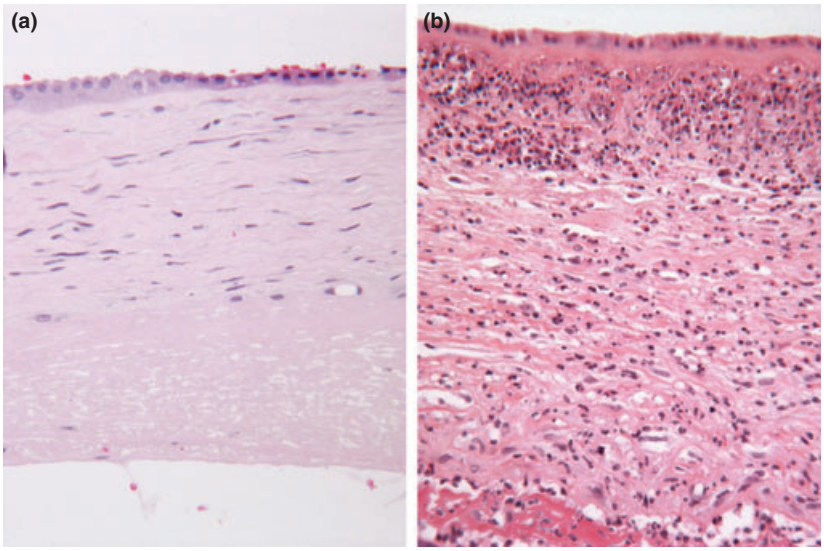

FIG. 1. Photomicrographs of a normal chorionic plate (a) and a chorionic plate with severe acute chorioamnionitis (b). Note the extensive neutrophil infiltration throughout the entire chorionic plate in the placenta affected by acute chorioamnionitis. Original magnification ×250. Photomicrographs courtesy of Dr Sarah Keating.

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and effectiveness of these biomarkers have not been confirmed in clinical trials. Other biomarkers, such as fetal fibronectin, relaxin, thrombin–antithrombin complex and salivary proteases, have also been investigated, but appear to be more specific in the prediction of PTB or PPROM than of chorioamnionitis [4].

As chorioamnionitis and intrauterine infection remain strong predictive markers of impaired cognitive and neurodevelopmental outcome [39,40], much research has revolved around the use of proteomic technology to identify biomarkers that may be used in the accurate diagnosis and prediction of neonatal outcomes in women with intrauterine inflammation [41–43]. Protein markers, including neutrophil defensin-1, defensin-2, calgranulin-A and calgranulin-C, have been associated with inflammation in the amniotic fluid and placenta. These have been correlated with stages of histological chorioamnionitis, grades of choriodeciduitis and amnionitis [44]. Furthermore, they have been associated with an increased risk of neonatal sepsis [45]. Currently, proteomics is a research technique, and is not used in clinical practice; however, future development of this technology and other diagnostic tests may prove to be important in determining patients at high risk of adverse outcomes from suspected intra-amniotic infection and chorioamnionitis.

In summary, owing to a lack of specific and sensitive tests that are safe for both mother and fetus, the diagnosis of chorioamnionitis is based predominantly on clinical signs and symptoms. Although amniocentesis is the most sensitive tool for culturing pathogens, its routine use is not recommended. The use of blood cultures, placental swabs and high vaginal swabs has yet to be shown to alter management and improve maternal and fetal outcome.

Treatment

Treatment of acute chorioamnionitis includes antimicrobial agents, antipyretics, expedition of delivery and management of additional symptoms. Despite the fact that chorioamnionitis is common, there is limited evidence to support one specific antibiotic regimen over another. The vast majority of studies, including several randomized controlled trials (RCTs), have used intravenous ampicillin 2 g every 6 h for coverage of Gram-positive organisms, intravenous gentamicin 1.5 mg/kg every 8 h for coverage of Gram-negative organisms, and intravenous clindamycin 900 mg every 8 h for additional coverage of anaerobes in the event of a caesarean section [37,46–48]. There is very little variation from this regimen in the literature with regard to intrapartum treatment. There is also little discussion of alternative drugs in the case of allergy, with one study using intravenous clindamycin 900 mg every 8 h as an alternative to ampicillin [37]. Metronidazole has also been reported as an alternative to clindamycin [46], and vancomycin or erythromycin as additional alternatives if the patient is allergic to penicillin [32]; however, there have been no RCTs to date comparing alternative regimens with the standard regimen of ampicillin and gentamicin.

The existing trials of antibiotic treatment have focused on variations in dosing and timing of drug administration and alterations to the spectrum of coverage. One RCT found a lower risk of postpartum endometritis in women treated with clindamycin in addition to ampicillin and gentamicin who had a vaginal delivery. There were no differences in women delivering by caesarean section [49]. A subsequent study showed a reduction in the risk of postpartum endometritis with additional anaerobic coverage at caesarean section (8.8% in the ampicillin–sulbactam group vs. 35% in the ampicillin-alone group) [50]. Thus, the recommendation was made to add anaerobic coverage for women with chorioamnionitis who are undergoing delivery by caesarean section [46].

In previous debates about the timing of treatment for chorioamnionitis, it had been argued that antibiotic treatment intrapartum may affect neonatal cultures, mask early neonatal sepsis and thus delay treatment, leading to poorer neonatal outcomes. This issue was addressed in the late 1980s, in a prospective cohort study and an RCT comparing intrapartum and immediate postpartum treatment with ampicillin and gentamicin. Although both studies were small, with 257 women in the cohort study and only 48 enrolled in the RCT, women who received intrapartum treatment had shorter hospital stays and improved neonatal outcomes, suggesting that intrapartum treatment is superior [47,51]. Despite the paucity of evidence, the current standard of practice is to initiate treatment with antibiotics promptly once the diagnosis of chorioamnionitis has been made. Although delivery should be expedited, caesarean section is still reserved for the usual obstetric indications [52].

Several trials have further investigated the benefits of extending treatment of intrapartum chorioamnionitis into the postpartum period beyond a single postpartum dose. One RCT randomized women delivering vaginally with a diagnosis of intrapartum chorioamnionitis to a single postpartum dose of cefotetan or continued cefotetan for a minimum of 48 h. No differences were shown between the groups in infectious morbidity, although the study was not powered to look at rare outcomes [53]. A study of single vs. multiple postpartum doses of clindamycin and gentamicin in women randomized after caesarean section also revealed no differ-

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ences in infectious morbidity. In particular, there was no difference in the rate of endometritis, the primary outcome. However, the predetermined sample size was not reached, and the study may thus have been underpowered to show a difference if one exists [54]. The largest randomized trial to investigate short-course vs. longer-course antibiotics postpartum after treated intrapartum chorioamnionitis was published in 2003, and enrolled 292 women. Participants were randomized to receive one additional scheduled dose of ampicillin and gentamicin postpartum or to the control group, who continued to receive ampicillin and gentamicin until they were afebrile and asymptomatic for 24 h postpartum. There were no significant differences in the primary outcome of treatment failure, and there were significantly shorter hospital stays in the study group [48], suggesting that prolonged antibiotic therapy postpartum does not provide additional benefit beyond a single dose and leads to increased costs.

More recently, trials of treatment of chorioamnionitis have shifted towards testing the efficiency and safety of once-daily dosing of gentamicin. Gentamicin is a commonly used aminoglycoside in pregnancy for the treatment of Gram-negative bacteria, although there is reluctance by some practitioners to use it, given the known side effects of renal toxicity and ototoxicity. It is well established that once-daily dosing has several advantages over multiple daily doses, with higher peak serum levels leading to increased efficacy of bacterial killing, and prolonged lower trough levels having a lower risk of toxicity [55]. Two recent randomized trials have studied daily vs. divided dosing of gentamicin for treatment of chorioamnionitis, and have found no differences in any adverse maternal or neonatal outcomes, although both studies were underpowered to detect small differences in neonatal sepsis or permanent infant hearing loss [56,57]. Further studies regarding these rare but important outcomes are required before a recommendation can be made to switch to once-daily dosing in labour.

Additional treatments in the management of acute chorioamnionitis include the antipyretic acetaminophen. A study of fetal acid–base balance showed significant improvements in intrapartum fetal heart rate monitoring as well as in bicarbonate and base excess values (based on scalp gases and cord gases) following treatment of intrapartum fever with acetaminophen [58]. Finally, although there has been previous concern about the use of regional analgesia in women with intrapartum fever, there does not seem to be any evidence of increased risk of harm (i.e. epidural abscess formation or meningitis) in women with chorioamnionitis receiving regional analgesia, even in those with no prior antibiotic administration [59,60].

Prevention

Strategies to prevent chorioamnionitis and subsequent adverse neonatal outcomes have focused on the identification and treatment of risk factors. One of the main risk factors for chorioamnionitis is PPROM, and there has been significant debate in the literature about whether antibiotic treatment of patients with PPROM will subsequently prevent chorioamnionitis and thus adverse neonatal outcomes. One of the largest trials to look at broad-spectrum antibiotic coverage for PPROM was the ORACLE I trial. This study did not have chorioamnionitis as a primary or secondary outcome; however, in women treated with erythromycin alone, neonatal outcome was improved, with prolonged rupture to delivery intervals, a decrease in the number of positive blood cultures and a trend to an improved neonatal composite score [61]. A recent Cochrane meta-analysis included several trials of antibiotic use in PPROM, and included chorioamnionitis as an outcome measure [62]. This meta-analysis revealed a significant reduction in the risk of chorioamnionitis with any antibiotic treatment (relative risk 0.66, 95% CI 0.46–0.96). There were also reductions in markers of neonatal morbidity, including neonatal infection, use of surfactant, oxygen therapy and an abnormal cerebral ultrasound finding prior to discharge [62]. Unfortunately, the fact that trials with different antibiotic regimens were all grouped together provides no guidance for the practitioner with respect to selecting a drug for prophylactic treatment.

One of the most common organisms isolated from both the lower genital tract and from placentas of women delivering prematurely is *U. urealyticum*. There is evidence that this bacterium is associated with PTB; however, the effectiveness of treatment with antibiotics is not clear. Evidence from a randomized trial suggests that treatment of *U. urealyticum* infection with erythromycin does not decrease vertical transmission, but it may prolong latency and decrease the risk of histological chorioamnionitis [63]. A further clinical study specifically powered to investigate the impact of treatment of *U. urealyticum* infection on the prevention of chorioamnionitis is warranted.

In the setting of intact membranes, the use of antibiotics, both as a preventive measure for PTB and as a treatment for subclinical/clinical vaginal infections, has been investigated. Clinical trials have shown no benefit of antibiotic treatment for the prevention of PTB in the absence of cultured infection [64], or even with documented microbial invasion of the amniotic cavity [65]. Another study of 2433 African women found no differences in the risk of chorioamnionitis in

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women treated with antibiotics prophylactically, although rates of *Trichomonas* and bacterial vaginosis did decline with treatment [66]. Although several international associations recommend treatment of bacterial vaginosis in pregnancy in women who are high risk, it is not clear that treatment itself reduces the risk of preterm labour through a reduction in intra-amniotic infection [67,68].

The use of vaginal irrigation and intra-amniotic infusion has also been studied for the prevention of chorioamnionitis, with varying results. Vaginal irrigation with chlorhexidine did not have any adverse effects, but was unsuccessful in reducing the risk of chorioamnionitis or endometritis in treated women [69]. Two small trials from the mid-1990s to late 1990s looked at amnio-infusion to reduce the risk of chorioamnionitis, and both showed a degree of benefit, although these studies were never followed with larger, appropriately powered, prospective RCTs [70,71].

Finally, there has also been a suggestion that antibiotic treatment of patients with meconium-stained amniotic fluid reduces intra-amniotic infection, although with no benefit in terms of lower rates of neonatal sepsis [72]. Currently, there is no clear evidence for or against this treatment.

Summary

Chorioamnionitis is a common obstetric problem, and if untreated can lead to significant maternal and neonatal morbidity and mortality. Chorioamnionitis is diagnosed on the basis of either clinical and/or histological findings. Once it has been identified, prompt treatment is recommended with broad-spectrum antibiotics, antipyretics, supportive care and expedition of delivery. Further research is needed to characterize the microbial communities found in the female genital tract, both in normal pregnancy and in pathological conditions such as chorioamnionitis. Similarly, further research is needed to identify screening and predictive investigations, with appropriate prospective validation of any potential test prior to its widespread use. Ongoing research on novel biomarkers may help to provide further information on the aetiology, causative pathways and potential interventions to help in the treatment and prevention of chorioamnionitis.

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Transparency Declaration

Conflicts of interest: nothing to declare.

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