Diagnosis and Management of Clinical Chorioamnionitis

Alan T.N. Tita, MD, PhD*, William W. Andrews, PhD, MD

KEYWORDS

• Chorioamnionitis • Infection • Pregnancy • Management

Chorioamnionitis is a common complication of pregnancy associated with significant maternal, perinatal, and long-term adverse outcomes. Adverse maternal outcomes include postpartum infections and sepsis whereas adverse infant outcomes include stillbirth, premature birth, neonatal sepsis, chronic lung disease, and brain injury leading to cerebral palsy and other neurodevelopmental disabilities. Research in the past 2 decades has expanded understanding of the mechanistic links between intra-amniotic infection and preterm delivery as well as morbidities of preterm and term infants. Recent and ongoing clinical research into better methods for diagnosing, treating, and preventing chorioamnionitis is likely to have a substantial impact on short and long-term outcomes in the neonate.

DEFINITION

Chorioamnionitis or intra-amniotic infection is an acute inflammation of the membranes and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of rupture of membranes (ROM). Chorioamnionitis can occur with intact membranes, and this seems especially common for the very small fastidious genital mycoplasmas, such as *Ureaplasma* species and *Mycoplasma hominis*, found in the lower genital tract of more than 70% of women.[1] Only rarely is hematogeneous spread implicated in chorioamnionitis, as occurs with *Listeria monocytogenes*.[2] When characteristic clinical signs are present, the condition is referred to as clinical chorioamnionitis or clinical intra-amniotic infection. Although there is

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Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, School of Medicine, University of Alabama at Birmingham, 619 19th South, Birmingham, AL 3524, USA
* Corresponding author.
E-mail address: alan.tita@obgyn.uab.edu

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significant overlap between clinical and histologic chorioamnionitis, the latter is a more common diagnosis based on pathologic findings on microscopic examination of the placenta that encompasses clinically unapparent (subclinical) chorioamnionitis and clinical chorioamnionitis. Funisitis, also a histopathologic diagnosis, is the extension of infection or inflammation to the umbilical cord. The definition of chorioamnionitis varies according to key diagnostic criteria, which can be clinical (presence of typical clinical findings), microbiologic (culture of microbes from appropriately collected amniotic fluid or chorioamnion), or histopathologic (microscopic evidence of infection or inflammation on examination of the placenta or chorioamnionic specimens).

EPIDEMIOLOGY (INCIDENCE AND RISK FACTORS)

Overall, 1% to 4% of all births in the United States are complicated by chorioamnionitis[2]; however, the frequency of chorioamnionitis varies markedly by diagnostic criteria, specific risk factors, and gestational age.[3–7] Chorioamnionitis (clinical and histologic combined) complicates as many as 40% to 70% of preterm births with premature ROM or spontaneous labor[8] and 1% to 13% of term births.[9–11] Twelve percent of primary cesarean births at term involve clinical chorioamnionitis, with the most common indication for cesarean in these cases being failure to progress usually after ROM.[12]

Several studies have reported risk factors for chorioamnionitis, including longer duration of ROM, prolonged labor, nulliparity, African American ethnicity, internal monitoring of labor, multiple vaginal examinations, meconium-stained amniotic fluid, smoking, alcohol or drug abuse, immunocompromised states, epidural anesthesia, colonization with group B streptococcus (GBS), bacterial vaginosis, sexually transmissible genital infections, and vaginal colonization with ureaplasma.[3–7,13–18] A strong association between untreated GBS bacteriuria and chorioamnionitis may reflect the high concentration of GBS in the genital tract.[19] After adjusting for potential confounding variables and depending on the specific confounders considered, some of the risk factors for chorioamnionitis identified in older studies no longer demonstrate an association in recent studies. Select factors independently associated with chorioamnionitis and their strength of association are summarized in **Table 1**.[3–7,13–17] Contrary to most obstetric conditions, chorioamnionitis in a previous pregnancy may not be associated with an increased risk of chorioamnionitis in a subsequent pregnancy.[20] Although preterm premature rupture of membranes (PPROM) is a major risk factor for clinical chorioamnionitis, together with preterm labor, PPROM frequently is the consequence of subclinical chorioamanionitis.[21]

MECHANISMS OF CHORIOAMNIONITIS AND ITS ASSOCIATED COMPLICATIONS

The pathogenesis of chorioamnionitis is marked by the passage of infectious organisms to the chorioamnion or umbilical cord of the placenta (**Figs. 1** and **2**).[21,22] This passage occurs most commonly by retrograde or ascending infection from the lower genital tract (cervix and vagina) (see **Fig. 1**). Hematogenous/transplacental passage and iatrogenic infection complicating amniocentesis or chorionic villous sampling are less common routes of infection. Anterograde infection from the peritoneum via the fallopian tubes has also been postulated.[22] The presence of infectious agents in the chorioamnion engenders a maternal and fetal inflammatory response characterized by the release of a combination of proinflammatory and inhibitory cytokines and chemokines in the maternal and fetal compartments (see **Fig. 2**). The inflammatory response may produce clinical chorioamnionitis or lead to prostaglandin release, ripening of the cervix, membrane injury, and labor at term or premature birth at earlier gestational ages. Aside from the risk of direct fetal infection and sepsis, the fetal

Table 1
Selected risk factors and their relative risks for chorioamnionitis

Risk Factor	Relative Risk	References
Prolonged ROM (including PPROM)		
≥12 Hours	5.8	13
>18 Hours	6.9	15
Prolonged labor		
Second stage >2 hours	3.7	15
Active labor >12 hours	4.0	14
Multiple digital examinations with ROM		
≥3 Examinations	2 to 5	13,14
Nulliparity	1.8	14
GBS colonization	1.7 to 7.2	14,16,19
Bacterial vaginosis	1.7	17
Alcohol and tobacco use	7.9	15
Meconium-stained amniotic fluid	1.4–2.3	7,14
Internal monitoring	2.0	13
Epidural anesthesia	4.1	15

inflammatory response may induce cerebral white matter injury, which may result in cerebral palsy and other short and long-term neurologic deficits (see **Fig. 2**).

Host defense mechanisms preventing intra-amniotic infection remain poorly elucidated, but specific local host factors likely play an important role. The cervical mucous plug and the placenta and membranes provide a barrier to infection of the amniotic

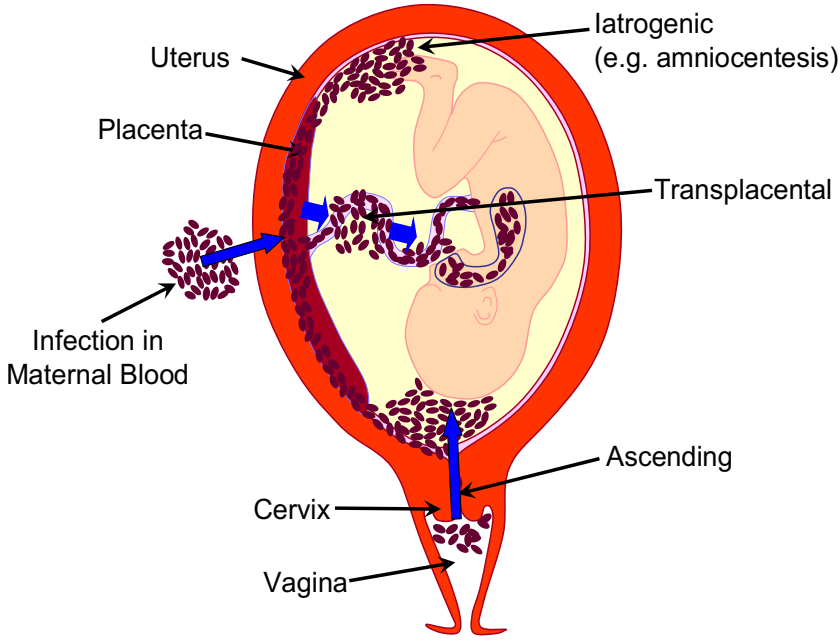

Fig. 1. Routes of chorioamnionitis/funisitis.

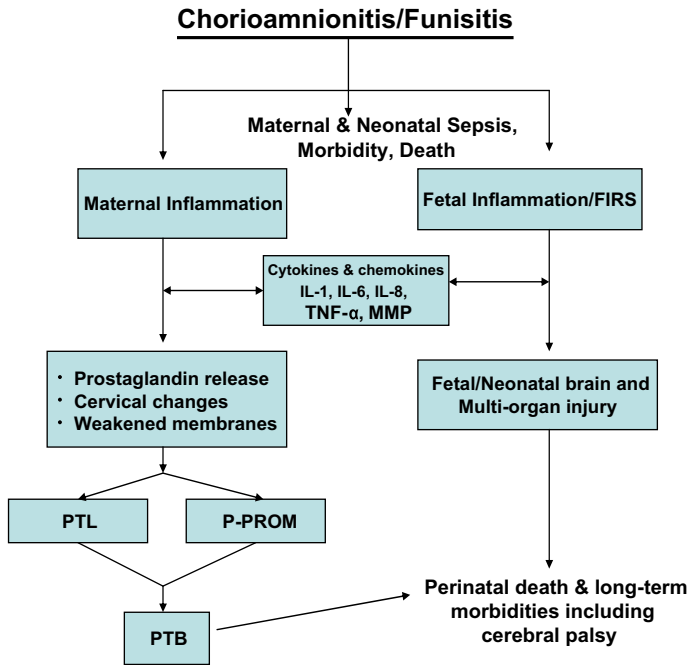

Fig. 2. Pathogenesis of chorioamnionitis: maternal and fetal response and complications. FIRS, fetal inflammatory response syndrome; IL, interleukin; MMP, matrix metalloproteinase; PTB, preterm birth; TNF, tumor necrosis factor.

fluid and fetus. Peroxide-producing lactobacilli in the birth canal may induce changes in the flora that impair the virulence of pathogenic organisms.

CLINICAL SIGNS AND SYMPTOMS

The key clinical findings associated with clinical chorioamnionitis include fever, uterine fundal tenderness, maternal tachycardia (>100/min), fetal tachycardia (>160/min), and purulent or foul amniotic fluid.[2,4]

Maternal fever is the most important clinical sign of chorioamnionitis. Temperature greater than 100.4°F is considered abnormal in pregnancy. Although isolated low-grade fever (<101°F) may be transient in labor, temperature greater than 100.4°F persisting more than 1 hour or any temperature greater than or equal to 101°F warrants evaluation and appropriate intervention. Fever is present in 95% to 100% of cases of clinical chorioamnionitis and typically is required for the diagnosis (discussed later). Fever in the setting of epidural anesthesia, particularly among nulliparous women with prolonged labor (so-called epidural fever), is often encountered and poses a diagnostic quagmire vis-à-vis chorioamnionitis.[23] This is because (1) in addition to fever, the 2 conditions share other major risk factors (low parity and prolonged labor); (2) epidural anesthesia masks signs of chorioamnionitis, such as fundal tenderness; and (3) medications given during epidural anesthesia may induce maternal or fetal tachycardia and, therefore, confound the diagnosis of chorioamnionitis.[24] The exact mechanism of epidural fever is unknown, but it is thought to be the result of epidural sympathetic blockade of thermoregulatory processes, such as sweating.[24] In one study, maternal fever was more common among the epidural group when placental inflammation was

present (35% vs 17%) but not in the absence of inflammation (11% vs 9%). This suggests that the pathologic basis for epidural fever is chorioamnionitis.[23] In sum, the concept of epidural fever remains controversial and warrants additional studies.

Maternal tachycardia (>100 beats per minute [bpm]) and fetal tachycardia (>160 bpm) occur frequently in chorioamnionitis, reported in 50% to 80% and 40% to 70% of cases, respectively. Tachycardia may be present in the absence of chorioamnionitis and requires careful assessment for alternative origins. Medications, such as ephedrine, antihistamines, and β-agonists, may raise maternal or fetal heart rate. The combination of maternal fever and maternal or fetal tachycardia is strongly suggestive, however, of intrauterine infection and should be treated accordingly.

Aside from the objective measurements of maternal fever and tachycardia, other signs of chorioamnionitis are highly subjective. Uterine fundal tenderness and a foul odor to the amniotic fluid are reported in only 4% to 25% of cases of chorioamnionitis.[4] Fundal tenderness is difficult to interpret in the context of the pain of labor and may be masked by analgesics, including epidural, or confounded by the pain associated with placental abruption. Purulence or foul odor of amniotic fluid is more likely present with severe or prolonged infection and may be organism-specific but may or may not be appreciated by clinicians.

Chorioamnionitis that is subclinical by definition does not present the clinical signs (discussed previously) but may manifest as preterm labor or, even more commonly, as PPROM. In addition, premature ROM at term (membrane rupture at ≥37 weeks' gestation but before onset of uterine contractions), which occurs in 8% or less of term births, is associated with an increased risk of chorioamnionitis.[25]

DIAGNOSIS OF CHORIOAMNIONITIS

Clinical

As suggested by the name, clinical chorioamnionitis is diagnosed solely based on clinical signs because access to uncontaminated amniotic fluid or placenta for culture is invasive and usually avoided. Typically, the presence of temperature greater than 100.4° is required in addition to 2 other signs (uterine tenderness, maternal or fetal tachycardia, and foul/purulent amniotic fluid).[2,4,26] Individual clinical criteria have variable sensitivity and low specificity for chorioamnionitis (**Table 2**). Because of the low specificity of clinical findings, consideration of other potential sources of fever and other causes of clinical symptoms is essential for the diagnosis of chorioamnionitis.[26] In the absence of other causes, the combination of 3 clinical criteria provides a highly accurate diagnosis of chorioamnionitis. The presence of risk factors of chorioamnionitis, especially ROM, further strengthens the diagnosis.

Laboratory Tests

Findings from laboratory or bedside testing may aid in ruling in or out the diagnosis of chorioamnionitis, particularly when the clinical signs and symptoms are equivocal (see **Table 2**).[2,27–32] Recent research on proteomic analysis for diagnosing intra-amniotic infection see the article by Irina Buhimschi and Catalin Buhimschi elsewhere in this issue for further exploration on this topic.

Complete blood cell count

Maternal leukocytosis (variously defined as white blood cell count >12,000/μL or >15,000/μL) or the presence of a left shift or bandemia (>9%) often supports the diagnosis of chorioamnionitis. Leukocytosis is reported in approximately 70% to 90% of cases of clinical chorioamnionitis. Isolated leukocytosis in the absence of other signs or symptoms, however, is of limited value because it may be induced by several other

Table 2
Clinical and amniotic fluid laboratory diagnosis of chorioamnionitis

Test	Result Suggesting Chorioamnionitis	Comments
Clinical parameters		Generally nonspecific[4]
Fever	Temperature >100.4°F twice or >101°F once	95%–100% sensitive[4]
Maternal tachycardia	>100/min	50%–80% sensitive
Fetal tachycardia	>160/min	40%–70% sensitive
Fundal tenderness	Tenderness on palpation	4%–25% sensitive
Vaginal discharge	Foul-smelling discharge	5%–22% sensitive
Amniotic fluid parameters		
Culture	Microbial growth	Diagnostic gold standard
Gram stain	Bacteria or white blood cells (>6/High Power Field)	24% sensitive, 99% specific[31]
Glucose level	<15 mg/dL	Affected by maternal hyperglycemia 57% sensitive, 74% specific[31]
IL-6	>7.9 ng/mL	81% sensitive, 75% specific[31]
Matrix metalloproteinase	Positive result	90% sensitive and 80% specific[30]
White blood cell count	>30/cubic mm	57% sensitive, 78% specific[31]
Leukocyte esterase	Positive (dipsticks)	85%–91% sensitive, 95%–100% specific[26,32]

conditions, including labor and steroid use. Therefore, routine monitoring of complete blood cell count in high-risk women (eg, those with PPROM) in the absence of clinical signs of chorioamnionitis is not useful.

Other blood tests

Other laboratory parameters, including high levels of C-reactive protein (CRP), lipopolysacharide-binding protein, soluble intercellular adhesion molecule 1, and interleukin (IL)-6, are associated with a higher risk of chorioamnionitis in the setting of PPROM or preterm delivery.[33–37] Their usefulness for the diagnosis or prediction of choriamnionitis, however, as part of routine clinical practice is not established.

Amniotic fluid testing

Tests on amniotic fluid, usually obtained by amniocentesis, have been used for the diagnosis of chorioamnionitis (see **Table 2**).[26,30–32] Culture of amniotic fluid is the most reliable test but is of limited use because culture results may not be available for up to 3 days. In addition, because of the invasive nature of the procedure, amniocentesis is not performed in the majority of cases of chorioamnionitis, which occur during labor. Some clinicians use amniocentesis to confirm clinically suspected chorioamnionitis to determine whether or not preterm delivery is warranted (thus avoiding iatrogenic prematurity). Amniocentesis is also used in some centers to identify subclinical chorioamnionitis in women with spontaneous preterm labor and preterm ROM at

early gestational ages. The value of this practice, however, has recently been questioned.[38]

Histologic chorioamnionitis captures subclinical and clinical chorioamnionitis; thus, it is not surprising that overall histologic chorioamnionitis at term is up to 3 times as frequent as clinical chorioamnionitis confirmed by amniotic fluid culture.[39] This is in part because cultures for genital mycoplasmas, the most common organisms associated with chorioamnionitis, are not very sensitive. Subclinical chorioamnionitis and noninfectious inflammation also contribute to this discrepancy. Histologic chorioamnionitis is defined by the presence of acute histologic changes on examination of the amnionic membrane and chorion of the placenta, and funisitis is characterized by leukocyte infiltration of the umbilical vessel wall or Wharton jelly.[8] Acute histologic changes are typically characterized according to the number of polymorphonuclear leukocytes per high power field or by detailed systems of staging/grading involving documentation of polymorphonuclear leukocyte location, density, and degeneration to estimate intensity and progression of chorioamnionitis.[40] Consequently, depending on the criteria used and maternal characteristics (including ethnicity and type of labor), the prevalence of chorioamnionitis based on placental pathology varies widely. Using varying thresholds of polymorphonuclear leukocytes per high-power field, the prevalence ranged from 7% to 85% in term and 4% to 63% in preterm deliveries in one study.[40] Overall, histologic chorioamnionitis is a sensitive (83%–100%) but not a specific (23%–52%) predictor of chorioamnionitis when the diagnosis is based on culture-positive amniotic fluid.[41] Alternatively, clinical chorioamnionitis is not uniformly confirmed on pathologic evaluation. In one study, only 62% of women with clinically diagnosed chorioamnionitis had histologic evidence of chorioamnionitis, leading to the speculation that noninflammatory causes, such as epidural fever and abruption, accounted for some of the cases.[42] For these reasons, placental pathology should be performed to confirm suspected chorioamnionitis even if amniotic fluid culture is negative. The pathologic finding of funisitis (inflammation of the umbilical cord) is even more concerning than chorioamnionitis alone because it represents a fetal response to infection. Although chorioamnionitis is present in nearly all cases of funisitis, funisitis is present in only up to 60% of cases of chorioamnionitis.[43]

Organisms Causing Chorioamnionitis

Chorioamnionitis is a polymicrobial infection most often due to ascending genital microbes[2,44]; more than 65% of positive amniotic fluid cultures involve 2 or more organisms. The genital mycoplasmas, *Ureaplasma urealyticum* and *M hominis* (genital mycoplasmas), constitute the most frequent microbes, occurring in up to 47% and 30%, respectively, of cases of culture-confirmed chorioamnionitis.[44,45] Their role in the pathogenesis of chorioamnionitis and neonatal complications, once controversial, is increasingly accepted.[46] These fastidious organisms provoke a robust inflammatory reaction affecting maternal and fetal compartments, particularly in preterm gestations.[45–47] They are commonly isolated from amniotic fluid in the setting of preterm birth or premature ROM with or without clinical chorioamnionitis.[46] Although genital mycoplasmas are found in the lower genital tract (vagina or cervix) of more than 70% of women, their presence in the upper genital tract (uterus or fallopian tubes) and chorioamnion of pregnant women is rare (<5%) in the absence of labor or ROM.[46–48]

Other common isolates in women with chorioamnionitis include anaerobes, such as *Gardnerella vaginalis* (25%) and bacteroides (30%), and aerobes, including GBS (15%) and gram-negative rods, including *Escherichia coli* (8%).[44] These organisms are commonly part of the vaginal flora (especially in women with bacterial vaginosis) or

the enteric flora (*E coli* and other gram-negative rods, enterococci, and anaerobes). An entity of aerobic vaginitis (distinguished from bacterial vaginosis in that it represents a strong host immune response to aerobic vaginal flora typically comprised of GBS and *E coli*) has been associated with ascending chorioamnionitis, PPROM, and preterm birth.[49] Occasionally, chorioamnionitis is the result of hematogenous spread of bacterial or viral infection to the placenta. *Listeria monocytogenes* infection of the fetus, which presents a pattern of early-onset and late-onset neonatal sepsis similar to GBS, is presumed due to a hematogenous route rather than an ascending infection.[50] More research is needed to clarify the significance of individual microbes and their potential interactions in the pathogenesis of chorioamnionitis. For clinical decision making and management, however, knowing the exact organisms involved in chorioamnionitis is not generally useful.

Other tests on amniotic fluid (see **Table 2**) are limited in their overall predictive abilities for chorioamnionitis, although the tests for IL-6 and matrix metalloproteinase are more promising because of higher sensitivity and specificity.[30–32] The use of vaginal pool fluid after premature ROM for these assessments (eg, glucose level) is rudimentary and warrants further investigation.[51]

Differential Diagnosis

Several other conditions should be considered in the differential diagnosis of chorioamnionitis. In intrapartum patients with epidural and low-grade fever without tachycardia (maternal or fetal) or other clinical signs of intrauterine inflammation, epidural-associated fever is a strong consideration. Extrauterine infections can cause fever and abdominal pain, during or in absence of labor, including urinary tract infection (pyelonephritis), influenza, appendicitis, and pneumonia. Noninfectious conditions associated with abdominal pain (usually in absence of fever) include thrombophlebitis, round ligament pain, colitis, connective tissue disorders, and placental abruption.

Complications of Chorioamnionitis

Clinical chorioamnionitis carries adverse consequences affecting women and their infants (see **Fig. 2**).

Maternal Complications

Chorioamnionitis leads to a 2- to 3-fold increased risk for cesarean delivery and a 2- to 4-fold increase in endomyometritis, wound infection, pelvic abscess, bacteremia, and postpartum hemorrhage.[12,52–55] The increase in postpartum hemorrhage seems due to dysfunctional uterine muscle contractions as a result of inflammation.[53,54] Ten percent of women with chorioamnionitis have positive blood cultures (bacteremia) most commonly involving GBS and *E coli*.[2] Fortunately, however, septic shock, disseminated intravascular coagululation, adult respiratory distress syndrome, and maternal death are only rarely encountered.[56]

Fetal Complications

Fetal exposure to infection may lead to fetal death, neonatal sepsis, and many other postnatal complications (see **Fig. 2**). The fetal response to infection—termed, *fetal inflammatory response syndrome* (FIRS)—may cause or aggravate some of these complications. FIRS is the fetal counterpart of the systemic inflammatory response syndrome (SIRS). Because clinical parameters analogous to those defining SIRS are difficult to ascertain in the fetus, FIRS was originally defined by elevation of cord blood IL-6 in the setting of preterm labor and PPROM[57,58] but can also occur in term gestations. The histopathologic hallmarks of FIRS are funisitis and chorionic

vasculitis.[59] FIRS is now recognized as representing the fetal immune response to infection or injury mediated by the release of cytokines and chemokines, such as interleukins, tumor necrosis factor α, CRP, and matrix melloproteinases.[58] FIRS has also been linked to preterm labor culminating in perinatal death (see **Fig. 2**) and is associated, particularly in preterm neonates, with multiorgan injury, including chronic lung disease, periventricular leukomalacia, and cerebral palsy,[60–62] Although FIRS may occur in the setting of noninfectious inflammation, its magnitude tends to be significantly more robust with documented infection.[63] Although somewhat controversial, fetal exposure to genital mycoplasmas (*U urealyticum* and *M hominis*) has been associated with a fetal and neonatal SIRS, pneumonia and bronchopulmonary dysplasia.[64–67]

Neonatal and Long-Term Complications

Neonates exposed to intrauterine infection and inflammation may show adverse effects at or shortly after birth. Adverse outcomes may include perinatal death, asphyxia, early-onset neonatal sepsis, septic shock, pneumonia, intraventricular hemorrhage (IVH), cerebral white matter damage, and long-term disability, including cerebral palsy.[9,68–72] In one study of term infants, neonatal pneumonia, sepsis, and perinatal death did not occur in the absence of chorioamnionitis but occurred, respectively, in 4%, 8%, and 2% of term deliveries associated with chorioamnionitis. In this study, respiratory distress occurred in 2% of term infants in absence of chorioamnionitis and 20% when chorioamnionitis was present.[68] Preterm infants have an even higher rate of complications of chorioamnionitis than term infants, including perinatal death (25% vs 6% preterm vs term), neonatal sepsis (28% vs 6%), pneumonia (20% vs 3%), grades 3 or 4 IVH (24% vs 8%), and respiratory distress (62% vs 35%).[69] Overall, chorioamnionitis is associated with up to 40% of cases of early-onset neonatal sepsis. Chorioamnionitis is also well established as a risk factor for long-term neurodevelopmental disability, especially when it occurs before term.[2,73–77] In term and near-term infants it is associated with a 4-fold increase in the frequency of cerebral palsy.[74,75]

Management of Chorioamnionitis

Prompt initiation of antibiotic therapy is essential to prevent maternal and fetal complications in the setting of clinical chorioamnionitis.[2] Time to delivery after institution of antibiotic therapy has been shown to not affect morbidities; therefore, cesarean section to expedite delivery is not indicated for chorioamnionitis unless there are other obstetric indications.[12,52,76]

Antibiotics

Evidence from randomized trials and observational studies demonstrate that immediate intrapartum use of broad-spectrum antibiotics significantly reduces maternal and fetal complications of chorioamnionitis.[77–81] The frequency of neonatal sepsis is reduced by up to 80% with intrapartum antibiotic treatment.[78,79] In a small randomized trial, neonatal sepsis occurred in none of 26 deliveries with intrapartum use of antibiotics compared with 21% of the 19 infants treated immediately postpartum.[77]

The optimal antibiotic regimen for treatment of clinical chorioamnionitis has not been well studied and current recommendations are based largely on clinical consensus.[81] Intravenous administration of ampicillin every 6 hours and gentamicin every 8 to 24 hours until delivery is the typical regimen.[81,82] If cesarean delivery is performed, clindamycin every 8 hours (or metronidazole) is often added for anaerobic coverage. Optimal treatment should also include administration of a single intravenous

additional dose of antibiotics after delivery (<5% failure rate)[83]; further oral antibiotic treatment is not beneficial in most cases.[84]

Although genital mycoplasmas are the most commonly isolated organisms associated with chorioamnionitis, the standard antibiotic regimens used for clinical chorioamnionitis do not provide optimal coverage against these organisms. Clindamycin does provide coverage against *M hominis* but none of the 3 standard antibiotics is effective against ureaplasma species, which is the most common group associated with infection. The standard regimen effectively treats maternal infection (>95% success rate) and reduces neonatal sepsis, and there are currently no published trials suggesting that specific coverage against ureaplasma (with macrolide antibiotics) provides additional benefits in the setting of chorioamnionitis.

Supportive measures

Supportive measures include the use of antipyretics (acetaminophen). This is particularly important during the intrapartum period because fetal acidosis in the setting of fever is associated with a marked increase in the incidence of neonatal encephalopathy.[85] Maternal fever even in the absence of documented fetal acidosis is associated with adverse neonatal outcomes, in particular neonatal encephalopathy, although it is unclear to what extent the etiology of the fever rather than the fever itself is causative.[86] Treating intrapartum fever with antipyretics may also be helpful in reducing fetal tachycardia, thereby avoiding the tendency to perform cesarean for a nonreassuring fetal status.

Prevention of Chorioamnionitis

Expectant management of PPROM is a major cause of clinical chorioamnionitis—up to 70% of those who subsequently develop contractions or labor have chorioamnionitis.[8] Prophylactic or latency antibiotics, typically ampicillin and erythromycin, have been demonstrated in large clinical trials (ORACLE I and II) and systematic reviews as conferring benefits, including reduction in a primary composite of neonatal death, chronic lung disease, or major cerebral abnormality on ultrasound. Antibiotics also reduce the incidence of clinical or pathologic chorioamnionitis and neonatal sepsis and prolong time to delivery among women with preterm ROM managed expectantly but not among those in active preterm labor with intact membranes (in whom maternal infection was reduced).[87–89] Amoxicillin/clavulanate antibiotic combinations should be avoided for this indication because of a potential association with an increased risk of necrotizing enterocolitis.[87–89] Furthermore, in the ORACLE II trial, the use of antibiotics for women with spontaneous preterm labor with intact membranes was associated with an unexpected increase in cerebral palsy in infants.[90,91] The findings were limited by potential selection bias (only 70% followed-up) and use of maternal report to ascertain outcomes (no direct examination). The investigators speculated that the findings could be due to chance or to maintenance of the fetus in a milieu with suppressed (not eradicated) subclinical infection given the low dose and oral route of antibiotics.[90,91] Another large trial conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network in the late 1990s suggested a benefit of erythromycin in reducing adverse perinatal outcomes, including perinatal death and morbidity and maternal infection.[92] No long-term follow-up data from this study are reported. The usual standard in the United States, therefore, remains the administration of broad-spectrum antibiotics, typically involving a macrolide (erythromycin or azithromycin) and ampicillin for 7 to 10 days via intravenous (2 days) followed by oral routes.[93] Induction of labor and delivery for PPROM after 34 weeks' gestation is recommended because, compared with expectant management, expeditious

delivery is associated with reduced maternal infection and need for neonatal intensive care without any increase in perinatal morbidity and mortality.[25,94,95] There is currently wide variation in practice, however, and additional trials are ongoing to firmly establish the benefit of induction of labor before 37 weeks in cases of PPROM.[25,96–98] In the setting of prolonged ROM (>18 hours) at term, prophylactic antibiotics are not indicated if the mother is not colonized with GBS; however, the CDC recommends starting GBS prophylaxis if GBS status is unknown.[99] In one randomized trial, the use of intrapartum prophylactic antibiotics (ampicillin/sulbactam) for meconium-stained fluid was associated with a reduction in the risk of chorioamnionitis.[100]

SUMMARY

Chorioamnionitis is a common infection of pregnancy, typically occurring in the setting of prolonged ROM or labor. It may be diagnosed clinically, based on signs, such as maternal fever; microbiologically, based on amniotic fluid culture obtained by amniocentesis; or by histopathologic examination of the placenta and umbilical cord. Chorioamnionitis is associated with postpartum maternal infections and potentially devastating fetal complications, including premature birth, neonatal sepsis, and cerebral palsy. The main preventative strategy is administration of antibiotics to women with PPROM, which reduces the incidence of clinical chorioamnionitis, prolongs the time to delivery, and improves neonatal outcomes. Optimal management of clinical chorioamnionitis includes antibiotic therapy and delivery. Shortening the time between diagnosis and delivery, however, by performance of cesarean section in the setting of broad-spectrum antibiotic administration has been shown not to improve outcomes.

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