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Chorioamnionitis: Implications for the Neonate Jessica

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Abstract

Chorioamnionitis (CA) is a perinatal condition characterized by inflammation of the fetal membranes. The incidence of CA increases with decreasing gestational age at birth. When CA is suspect based on clinical criteria, pathologic assessment of the placenta should be performed. While the mechanisms are not entirely clear, CA predisposes infants to premature birth, neonatal sepsis and intraventricular hemorrhage. The role of CA in respiratory distress syndrome, bronchopulmonary dysplasia, and neurodevelopmental impairment is mixed. Prevention and treatment of CA are not well defined. The use of antibiotics for preterm premature rupture of membranes reduces the incidence of CA and increases the length of time to delivery. Antibiotics are recommended for infants exposed to CA while laboratory studies are being performed.

Keywords

neonatal sepsis; fetal inflammatory response; *Mycoplasma*

Chorioamnionitis (CA) is a perinatal condition characterized by inflammation of the fetal membranes: the chorion and amnion. The incidence of CA increases with decreasing gestational age at birth. Ascending bacterial infection is thought to be the primary mode of acquisition; viruses and fungi are rarely implicated. While the mechanisms are not entirely clear, CA predisposes infants to premature birth, neonatal sepsis, and other adverse outcomes. In this manuscript, we will review the pathophysiology of CA (including definitions), risk factors for CA, management strategies for CA, and neonatal outcomes.

Definition

The definition of CA is inconsistent between clinicians and across epidemiologic studies, and this inconsistency has contributed to the conflicting associations between CA and fetal outcomes. The most rigorous definition of CA is inflammation of the chorionic and amniotic layers of the fetal membranes confirmed by pathologic review of the placenta[1] (Table 1).

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The pathologic diagnosis requires the presence of a neutrophilic infiltrate to be present in the placental tissues. Early studies used a threshold of 10 neutrophils per high power field in at least 10 fields as a definition for histologic CA.[2] More recently, the Extremely Low Gestational Age Newborn (ELGAN) Study group graded the severity of inflammation of each membrane and considers CA to be present when >20 neutrophils are present per 20× field of the chorion or the presence of numerous large or confluent foci of neutrophils or necrosis of the amnion.[1]

Recently, attempts have been made to distinguish between involvement of only the maternal portion of the placenta and inflammation that involves both the maternal and fetal portions as there appear to be differences in neonatal outcomes for infants with more proximal inflammatory changes.[3-6] Inflammation that involves the fetal portion is often referred to as fetal inflammatory response (FIR).[6] CA can be further complicated by involvement of the umbilical cord, a condition called funisitis.[7] Investigators from the ELGAN study group consider funisitis to be present when there is fetal vasculitis with neutrophils noted in the perivascular Wharton's jelly.[1] Funisitis is evidence of a vigorous fetal response, and thus is considered a “severe” form of CA. However, even the pathologic diagnosis can vary, depending on how long the placenta was at room temperature before refrigeration, where the placental tissue was sampled, and the skill of the pathologist.

Some investigators define CA as the isolation of bacterial or fungal organisms from the placenta or amniotic fluid, regardless of the presence of inflammation. Histologic CA and the isolation of organisms are highly associated but can occur separately.[2] Organisms can be isolated by culture or polymerase chain reaction (PCR) (Table 2). Placental cultures may be negative even in the presence of overt histological inflammation.[8] One study found that only 4.6% of placental cultures revealed an organism when culture was performed for indications of preterm delivery, prolonged rupture of membranes, suspected infection or fetal death.[9] This is likely due to difficulty culturing fastidious or intracellular organisms such as *Mycoplasma* and *Ureaplasma* species' or low colony counts. PCR has been used successfully to increase sensitivity but also fails to detect all pathogens.[10,11] When 150 placentas were cultured and tested via PCR, 141 had no organisms, 10 had organisms detected by both PCR and culture; PCR alone was positive in 9 cases and culture alone was positive in 6 cases.[12] Fastidious organisms were more likely to be identified by PCR. PCR failed to detect coagulase-negative *Staphylococcus* species, *Bacillus* species, *Peptostreptococcus* species and *Gardnerella vaginalis*.[12] Anaerobic and mixed infections are common which can complicate detection by culture and PCR.[13]

Due to laboratory limitations, the diagnosis of CA is often made clinically. Fever, uterine tenderness, maternal or fetal tachycardia, maternal leukocytosis, and foul smelling uterine discharge are commonly considered to represent CA.[14] These findings are nonspecific, however, and have variable relation to histologic CA. Using histologic CA as the reference standard, the sensitivity of maternal fever was only 42%.[15] Maternal tachycardia and fetal tachycardia were 47% and 36% sensitive respectively.[15] The sensitivity of clinical signs increased to 60% when maternal tachycardia, uterine tenderness, maternal leukocytosis or malodorous amniotic fluid was present in addition to maternal fever.[16] A study that evaluated placental tissue from 2774 pregnancies found that maternal fever was absent in

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92% of histologic CA cases.[17] Conversely, of women with peripartum fever, 59% had findings of CA.[17] The variability and limited sensitivity of findings used to diagnose CA clinically makes comparison of studies and outcomes more difficult.

Inflammatory changes themselves may have a stronger association with adverse outcomes, including preterm birth, than the presence of microorganisms alone.[18] Intra-amniotic interleukin-6 (IL-6) predicts both preterm birth and neonatal morbidity. Investigators found that mothers presenting in preterm labor with amniotic fluid IL-6 levels > 11.3 ng/ml delivered after a median of 1 day; those without elevated IL-6 levels delivered after a median of 25 days.[10] Another cohort of 261 very low birth weight (VLBW, <1500 g birth weight) infants found a C-reactive protein elevated > 10 mg/L was significantly more common in the 99 infants exposed to CA (25% vs 11%, p=0.005).[19] For 799 infants born <27 weeks gestation, infants exposed to CA were more likely to have an elevated C-reactive protein, OR= 5.3 (95% confidence interval; 3.0, 9.6), as well as elevation of other cytokines.[3] Inflammatory markers may add objective information to the clinical criteria used in diagnosis when pathological information is unavailable.

Pathophysiology

The introduction of organisms into the fetal membranes and the placenta is thought to occur via four anatomic pathways. The first, and most common, mechanism is ascending infection through the maternal genital tract. Vaginal and enteric floras are often implicated with this route of infection.[20] Second, iatrogenic inoculation can occur following invasive procedures such as amniocentesis.[21] Third, hematogenous spread can occur with migration of organisms from the maternal bloodstream across the placenta.[22] *Listeria monocytogenes* in particular has been described to cause infiltration of the placenta following maternal infection.[23] Fourth, and least common, peritoneal infections can enter the intrauterine space via the fallopian tubes. Mothers with chronic kidney or liver disease are most at risk for infection by this mechanism.[24]

Ascending infection can ultimately result in disease of the fetal membranes. Preterm and prolonged rupture of membranes has been associated with increased risk of CA.[4] This may be because removal of the anatomic barrier provided by intact membranes allows for easier migration of organisms from the maternal genital tract into the fetal tissues. Conversely, the membranes may rupture due to the apparent tendency of infection to weaken the membranes, predisposing them to rupture.[25] Separating which of these is the primary cause of CA is often challenging.

Neonatal Outcomes

Preterm Birth

Preterm birth is the most consistently demonstrated consequence of CA.[26] An early prospective observational study of 2774 mother-infant pairs found that as many as 25% of preterm births are attributable to CA.[17] This was later confirmed in a case-control study demonstrating that premature infants have significantly increased odds of both bacterial isolation and histologic findings of CA. [2] A recent prospective study of 871 pregnancies

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found that of those with histologic CA, premature delivery occurred nearly twice as often as those without CA.[27] When *Ureaplasma urealyticum* was detected following preterm premature rupture of membranes of 154 pregnancies, the median gestational age at delivery was 4 weeks less than when it was not detected.[11] Of 50 women who presented in preterm labor with intact membranes, elevated intra-amniotic levels of the proinflammatory cytokines IL-6, interleukin-1, prostaglandin E2 and tumor necrosis factor alpha were associated with progression to preterm birth.[28]

Neonatal Sepsis

Infants born following CA are at increased risk for neonatal infection. Organisms infecting the chorionic membranes are in close proximity to the fetus and can cause fetal infection as a natural consequence of this proximity. The organisms that most often cause early onset neonatal sepsis are those that are also frequent causes of CA: *Escherichia coli* and group B *Streptococcus*.[29] Exposure to CA appears to confer a risk of early onset sepsis of 1-3%[17], 10 times higher than the overall risk of early onset sepsis.

Premature infants are particularly susceptible to sepsis following CA. A case control study found that VLBW infants exposed to CA had significantly increased odds of early onset sepsis, OR= 4.7 (1.4, 15.9), p=0.015.[30] For infants <32 weeks gestational age, 145 infants exposed to histologic CA developed clinical criteria consistent with sepsis syndrome significantly more often than 136 infants without CA, 39% vs 24% (p=0.007).[31]

Term infants are also at risk for neonatal infection following CA. Of 5144 term infants exposed to CA, 1.3% developed culture proven neonatal sepsis, OR=2.9 (2.1, 4.1)[32]. An analysis of 3094 births found that a clinical diagnosis of CA was independently associated with increased odds of early onset neonatal sepsis even with adjustment for initial severity of illness and baseline characteristics, OR=5.54 (2.87, 10.69), p<0.001.[33]

Funisitis seems to confer a higher risk of sepsis. When 315 preterm births were considered, 12% of infants with funisitis had a positive blood culture within 72 hours of delivery compared to 1% of infants without funisitis, OR=7.2 (1.8, 29.0).[34] A prospective observational study of 231 infants found that early onset sepsis occurred in 18% of infants with funisitis compared to 4% of infants without funisitis, p=0.002.[7]

Brain Disease

CA is associated with an increased incidence of early neurologic insults, including severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), which are established causes of neurodevelopmental impairment in premature infants. A multicenter study of Canadian Neonatal Network hospitals found that CA increased the odds of severe IVH even after adjusting for severity of illness, OR=1.62 (1.17, 2.24).[33] The presence of mononuclear inflammatory cells in the fetal membranes has been found to be associated with increased severe IVH even after controlling for gestational age, OR=8.9 (2.1, 37.9).[35] A study of 1367 VLBW infants found that exposure to clinical CA increased the odds of both IVH, OR=2.8 (1.6, 4.8), and PVL, OR=3.4 (1.6, 7.3).[36] Recently, inflammatory changes that were classified as FIR were found to increase the odds of grades II-IV IVH,

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OR=4.1 (1.3, 13.2).[5] However, for the 53 pregnancies where inflammation was isolated to only the maternal placental tissues there was no increase in IVH compared to the 112 with no placental inflammatory changes, OR=0.9 (0.2, 3.7).[5]

Even when a perinatal diagnosis of IVH or PVL is not documented, CA appears to be associated with an increased risk of cerebral palsy. A case control study of 424 infants with birth weights > 2500 g found that both clinical CA and histological evidence of placental infection were associated with significantly increased odds of spastic cerebral palsy.[37] Similarly, 18 month developmental testing of 33 infants exposed to clinical CA was significantly worse in cognitive, language and motor domains than 146 control infants even though the incidence of PVL and grade III-IV IVH were similar between the 2 groups.[38] The relationship between CA and neurodevelopmental impairment may partially be due to the intermediate of neonatal sepsis, which has a well described role in neurodevelopmental impairment.[39-41] However, exposure to inflammatory cytokines likely exerts direct damaging effects on the developing brain.[42-45]

The relationship between CA and poor neurodevelopmental outcome has not been demonstrated in all studies. For 39 infants born <32 weeks gestation who were exposed to CA compared to 33 control infants, there was no difference between groups in mental and psychomotor developmental indices.[31] Similarly, a case control study found no difference in performance on the Bayley Scales of Infant Development between the 71 infants exposed and the 259 infants not exposed to CA at 7 months corrected age.[30]

Lung Disease

The relationship of CA and neonatal pulmonary morbidity is conflicting. Various studies have evaluated the risk of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) following exposure to CA.

Respiratory distress syndrome

CA has been associated with a lower incidence of RDS in some studies. A lower incidence of RDS in infants exposed to CA may occur because exposure to prenatal inflammation appears to accelerate lung development and stimulate surfactant production. This rationale is supported by a study that found that RDS was significantly less common in infants exposed to CA than their unexposed counterparts, relative risk (RR)=0.56 (0.34-0.90).[46] A more recent multivariable analysis of 301 premature infants similarly found that CA decreased the odds of severe RDS.[47] Infiltration of the fetal membranes by polymorphonuclear cells was associated with a lower incidence of RDS in infants <32 weeks gestational age, OR=0.4 (0.3-0.7).[35] Another study of 216 infants considered inflammation of the maternal aspect of the placenta alone versus inflammation on the maternal and fetal aspects as 2 distinct pathologies.[5] They found that FIR conferred a protective effect with a reduced odds of RDS compared with placentas with no inflammation or with inflammatory changes only of the maternal placental tissues, OR=0.08 (0.01-0.62).[5]

However, several studies have found an increase in RDS associated with CA. One study of 95 infants with mean gestational age of 34 weeks found 0 cases of RDS among infants

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without histologic CA; 23% of infants exposed to CA developed RDS.[48] RDS was also observed more frequently in infants exposed to clinical CA than those who were not in a study of 1367 VLBW infants, OR=2.9 (1.5, 5.5).[36] A multicenter analysis of 3094 infants did find that RDS was more common after CA on univariable analysis but when gestational age and birth weight were included in a multivariable model, the relationship was no longer significant.[33] A study of 1340 infants <27 weeks gestation also found no association between histologic CA or the detection of organisms and respiratory status during the first 2 weeks of life.[49]

Bronchopulmonary dysplasia

The relationship between BPD and CA is also conflicting. The rationale for an increased risk of BPD following CA is that intrauterine exposure to inflammation may cause subsequent lung development to be abnormal leading to BPD.[50] In 1996, the first publication supporting an increased incidence of BPD following CA found a RR=2.18 (1.07, 4.43) for BPD in infants with birth weights <2000 g exposed to CA.[46] A meta-analysis including studies from 1994-2009 found that histological, but not clinical, CA was associated with an increased odds of BPD, OR=2.19 (1.76, 2.72).[51]

Data that are not supportive of an association between CA and BPD include a histological evaluation of 446 placentas that failed to find a difference in BPD incidence for those with and without inflammatory cell infiltration.[35] Evaluation of 529 infants born < 29 weeks gestation found that histological CA with FIR was associated with a decreased incidence of BPD, RR=0.88 (0.81, 0.95).[4]

Management of CA

Prenatal Antibiotics

Randomized, controlled trials support the use of antibiotics in women who present with preterm premature rupture of membranes. Six hundred and fourteen women with rupture of membranes between 24 and 32 weeks gestation were randomized to treatment with amoxicillin (or ampicillin IV) or placebo.[52] More women treated with antibiotics were still pregnant at 2 (p=0.03), 7 (p=0.001), 14 (p=0.001) and 21 (p=0.008) days than those given placebo.[52] Infants born to mothers treated with antibiotics had less RDS, RR=0.83 (0.69, 0.99), necrotizing enterocolitis, RR=0.40 (0.17, 0.95), and BPD, RR=0.64 (0.45, 0.92) than those given placebo.[52] A recent Cochrane review found that use of antibiotics following preterm premature rupture of membranes decreased the risk of delivery within 7 days of rupture, RR=0.79 (0.71, 0.89), decreased the incidence of neonatal infection, RR=0.67 (0.52, 0.85), and reduced the incidence of CA, RR=0.66 (0.46, 0.96).[53]

For rupture of membranes occurring after 36 weeks gestation, a recent randomized trial found no reduction in the incidence of early onset sepsis, the need for mechanical ventilation or fetal death for 820 infants exposed to prenatal antibiotics compared to 820 infants exposed to placebo, RR=1.42 (0.85, 2.37).[54]

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Postnatal Antibiotics

Due to the elevated risk of early onset neonatal sepsis in infants exposed to CA, the Committee on the Fetus and Newborn (COFN) of the AAP has recommended that infants exposed to CA have laboratory studies performed and be started on empirical broad-spectrum antibiotics.[55,56] If studies are normal, cultures are negative and the infant is doing well, antibiotics should be stopped at 48 hours.[55] Similarly, the CDC has recommended that infants exposed to CA be started on empirical antibiotics and undergo laboratory evaluation including blood cultures.[57] Neither the AAP nor the CDC make a recommendation regarding duration of therapy. If the infant is clinically well and cultures are negative but the complete blood count or C-reactive protein is suggestive of infection, the role of additional or prolonged antibiotic treatment is unclear.

Antenatal Steroids

The benefits of antenatal steroid administration for preterm delivery are well described. For infants exposed to CA, antenatal steroids also improve outcomes. Exposure to antenatal steroids significantly decreased the incidence of both severe IVH and mortality for 53 infants with histologic CA.[47] A Japanese Neonatal Research Network study of 7896 infants <34 weeks gestational age with histologic CA similarly found that RDS (OR=0.72, $p<0.001$), IVH (OR=0.68, $p<0.001$) and mortality (OR=0.50, $p<0.001$) occurred significantly less often in infants whose mothers received antenatal corticosteroid therapy.[58]

Conclusion

CA is a common problem, especially among preterm deliveries. Diagnosis is most accurately made from pathological specimens. For preterm premature rupture of membranes, antibiotics should be used to reduce the risk of preterm birth and its subsequent complications. Antibiotic administration to infants born following CA is recommended. Future studies should explore improved diagnostic and treatment modalities.

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Key Points

- Chorioamnionitis is a pathologic diagnosis that is suggested by clinical findings.
- Neonatal sepsis occurs in 1-3% of infants exposed to chorioamnionitis.
- Infants exposed to chorioamnionitis require additional monitoring and testing.
- Exposure to chorioamnionitis may lead to a variety of adverse neonatal outcomes but a causal relationship has been difficult to consistently demonstrate.

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Best Practices Box

What is the current practice?

- Various strategies used to define chorioamnionitis
- Most infants exposed to chorioamnionitis are evaluated for signs & symptoms of infection

Major Recommendations

- Screen infants exposed to CA with complete blood count & blood culture
- Evaluate the placentas of infants born prematurely or following prolonged rupture of membranes for evidence of CA
- Mothers with preterm premature rupture of membranes should receive antibiotic therapy

Summary Statement

CA predisposes infants to premature birth, neonatal sepsis and IVH; the role of CA in RDS, BPD, and neurodevelopmental impairment is unclear. Antibiotics for preterm premature rupture of membranes reduces the incidence of CA. Antibiotics are recommended for infants exposed to CA while laboratory studies are being performed.

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Table 1

Definitions of chorioamnionitis

Histologic CA	Pathologic diagnosis, inflammatory cells are present in the fetal membranes[19,59]
Clinical CA	Typically maternal fever + at least 2 of: uterine tenderness, fetal or maternal tachycardia, maternal leukocytosis, foul smelling amniotic fluid[15,52]
Maternal inflammatory response	Inflammatory changes limited to the subchorion, chorion and amnion[5]
Fetal inflammatory response	Umbilical vasculitis, funisitis, elevated inflammatory markers in the cord blood[5,60]

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Table 2

Organisms commonly identified in chorioamnionitis.

Organism	Prevalence	Reference
Ureaplasma urealyticum	15-62%	18,28,61-63
Mycoplasma hominis	7-35%	18,61-63
Group B *Streptococcus*	8-11%	62,64
Escherichia coli	7-12%	62,64
Gardnerella vaginalis	8-25%	28,64
***Bacteroides* sp**	8-30%	64
***Fusobacterium* sp**	10-67%	28,64
***Prevotella* sp**	17%	64
***Peptostreptococcus* sp**	16%	64