HISTOLOGICAL CHORIOAMNIONITIS: CURRENT CONCEPTS OF DIAGNOSIS, CLASSIFICATION AND CLINICAL SIGNIFICANCE

1F JESSOP AND 2NJ SEBIRE

1Departments of Paediatric Pathology, Addenbrookes Hospital, Cambridge, 2Great Ormond Street Hospital, London

INTRODUCTION

Interest in the clinical associations between maternal intrapartum fever and adverse neonatal outcome has been longstanding, with publications of a relationship between maternal fever and cerebral palsy dating from the 1950s.1 Further recognition of the associations between either clinically or histologically characterised chorioamnionitis, ascending infection and neonatal wellbeing followed, with numerous reports in the 1960s and 70s,2,3 particularly as the neonatal significance of group B streptococcal infections became apparent.4 Similarly, with the systematic introduction of diagnostic light microscopy into clinical medicine, chorioamnionitis (inflammation of the placental membranes) and funisitis (inflammation of the umbilical cord) were recognised as distinct histological entities, with increasing recognition that the aetiology was likely to be infective.5 There are numerous texts discussing in detail the pathogenesis and histological features of chorioamnionitis and funisitis.3,5,6 The aim of this review is to provide an overview of the salient associated issues for clinical practitioners and to highlight areas of ongoing uncertainty and recent developments in understanding.

Initial suspicion of chorioamnionitis and funisitis may be raised by clinical observation and simple laboratory investigations during labour (‘clinical chorioamnionitis’). Histological diagnosis is, however, based on examination of haematoxylin and eosin [H&E] stained sections of membranes and cord examined by light microscopy, (‘histological chorioamnionitis’). Whilst these entities overlap, they are not synonymous and across all gestations, the relationship between clinical and histological chorioamnionitis is relatively poor. Although chorioamnionitis and funisitis are well described, there remain many uncertainties surrounding their diagnosis and in particular regarding the clinical significance of their presence,
principally due to the presence of two apparent coexisting paradoxes. First, that positive maternal symptoms and laboratory findings are quite frequently not associated with evidence of membrane or cord inflammation, and secondly, that inflammation is not uncommonly present in placentas from asymptomatic mothers where neonatal outcome is unremarkable. In this review, we summarise current knowledge, identifying areas of apparent consensus while highlighting those areas which remain controversial or require further investigation.

AETIOLOGY AND PATHOGENESIS OF CHORIOAMNIONITIS AND FUNISITIS

Chorioamnionitis and funisitis are now generally accepted to be attributable to infection, almost always ascending genital tract infection, with formal recognition of this process dating back many decades. Alternative hypotheses have been suggested, including that the observed inflammation may be attributable to hypoxia or cellular damage caused by meconium staining, but have not been corroborated either by historical or more recent studies and the weight of evidence for an infective aetiology is substantial. Some of the putative objections to infection being the aetiologic agent are derived from limitations of current standard clinical investigations for detecting infection, for example studies have been based on evidence from placental or high vaginal swabs taken at delivery. There is good evidence that these investigations are insensitive to detect infection, with amniocentesis samples having been suggested as a more sensitive and specific test for amniotic fluid infection than placental cultures. Multiple studies have now demonstrated increased detection of various species using PCR based techniques compared to cultures.

In addition, observations in twin pregnancies provide further evidence both supporting infection and refuting hypoxia as a possible aetiological event in the development of chorioamnionitis. In twin pregnancies, indisputably hypoxic events such as infarcts or cord accidents are not accompanied by chorioamnionitis, whereas chorioamnionitis always preferentially affects the presenting twin which is overlying the cervicval os, and a gradient response is present with the presenting twin associated with much more florid inflammation than the second twin. The hypothesis that meconium within amniotic fluid may induce chorioamnionitis was suggested based on the concept that inflammation can be a response to cellular damage due to any cause; in the case of meconium, chemical injury is hypothesized. This is not however supported by any experimental evidence and is generally considered unlikely, especially since most cases of meconium passage are not associated with histological chorioamnionitis.

Finally, the cellular pattern of inflammation observed in cases of histological chorioamnionitis, with large numbers of neutrophil polymorphs present demonstrating a clear gradient of density due to chemotaxis, is typical of an acute infectious aetiology at other sites.

When considering specific microbial species which have well-documented associations with chorioamnionitis and funisitis, data primarily implicate those...
inhabiting the lower female genital tract during pregnancy, such as enterococci, coagulase positive staphylococci, anaerobic streptococci and E.coli. Most of these organisms are familiar in routine clinical obstetric and gynaecological practice. Group B streptococcus, which intermittently colonises the lower female genital tract and rectum, has been particularly intensively investigated since it may be associated with potentially severe perinatal morbidity and mortality. While there is limited historical evidence correlating neonatal streptococcal infection with histological chorioamnionitis, evidence from large screening programmes positively associates untreated antepartum group B streptococcal bacteriuria in the first 20 weeks of pregnancy with chorioamnionitis at delivery. Occasionally, other, less common, bacterial species are reported, for example Haemophilus influenzae, Neisseria gonorrhoea and Streptococcus pneumoniae, but the mode of transmission for most bacteria, whether commonly or occasionally reported is almost always ascending from the lower female genital tract.

Mycoplasma and ureaplasma are smaller than conventional bacteria, but both ureaplasma and mycoplasma hominis may be present in the lower genital tract of sexually active adults; ureaplasma being more common. Their frequency is probably under-reported in routine clinical practice, due to the relative fragility of the organisms requiring specific methods for their detection, and uncertainties in differentiating asymptomatic colonization from true pathogenicity. There is, however, evidence that both mycoplasma and ureaplasma infections can in some cases be directly associated with amniotic inflammation, and also that they can cross intact membranes relatively early in pregnancy. Premature infants appear to be particularly at risk of significant sequelae of ureaplasma chorioamnionitis.

Fusobacterium sp, which are most commonly identified within the oral cavity, have been reported in association with clinical intra-uterine infection, preterm birth and histological evidence of inflammation in the delivered placenta via haematogenous transmission. Other organisms, for example Bergeyella sp present within subgingival plaque, have also been identified as organisms which may be disseminated to the uterine cavity haematogenously. More recently, it has been suggested that bacterial colonization of the oral cavity, (without necessarily involving translocation of organisms to the uterine cavity), may predispose to premature birth possibly via pathways involving release of circulating factors such as prostaglandins and tumour necrosis factor. However, systematic data regarding a possible relationship with an inflammatory reaction in the placenta remains undocumented. Most haematogenous infections result in villitis or intervillositis rather than chorioamnionitis but rarely infections with unusual bacteria found in the oral cavity are associated with chorioamnionitis in single case reports but these appear to originate from alternative forms of transmission, namely orogenital sexual transmission.

Fungal infections associated with chorioamnionitis are rare, and almost always due to candida albicans. This organism is, of course, frequently identified in the vagina despite ascending candidal infection being relatively rare, possibly due to inhibitory effects of amniotic fluid. Viruses, primarily Herpes simplex virus, have
very rarely been reported in association with chorioamnionitis, based on recognition of membrane/cord inflammation in association with herpetic vesicles.\textsuperscript{34} PCR based studies have, however, identified specific viral sequences from CMV, HPV subtypes and adenovirus in cases of histological chorioamnionitis from woman presenting with second trimester pregnancy loss, although causation remains unproven.\textsuperscript{35}

The host response to the presence of microbial agents is increasingly recognized to be a primary event in the development of clinically significant chorioamnionitis.\textsuperscript{36} The pathways which mediate the effects of ascending infection are not entirely understood, although clearly of interest in terms of potential interventions. Separate components of the immune response have been examined in various studies, identifying areas which are at least potentially important in mediating the effects of infection. Currently, there is interest in Toll-like receptors (TLRs), which are expressed by a range of cells, epithelial, monocyte/macrophage and dendritic, and form part of the innate immune system, recognizing both gram positive and gram negative organisms. Both TLR 2 (which recognizes gram positive bacteria) and TLR 4 (which recognizes gram negative bacteria) are expressed in amniotic epithelium in labour and associated with histological chorioamnionitis.\textsuperscript{37} Ligation of TLRs results in intracellular transcription of a range of biologically active peptides, including cytokines, which may induce further development of a maternal and fetal immune response. For example, pentraxin 3, which is stored in neutrophils, is released in response to a number of pro-inflammatory signals including TLR engagement and raised amniotic fluid pentraxin 3 levels are associated with histological chorioamnionitis.\textsuperscript{38} Other components of the inflammatory response cascade include the receptor for advanced glycation end products (RAGE) and its stimulatory and inhibitory ligands, soluble RAGE (sRAGE) and endogenous secretory RAGE (esRAGE). Activation of the RAGE system has proinflammatory effects, and the RAGE system has been demonstrated to be upregulated in chorioamnionitis.\textsuperscript{39,40} Recently, polymorphisms in both maternal and fetal genes known to be associated with inflammatory pathways have been identified in large candidate gene association studies of preterm birth and preterm premature rupture of membranes.\textsuperscript{41,42}

The tissue reaction to infection is documented by light microscopic examination of the placenta, and traditionally this has been the “gold standard” for the diagnosis of chorioamnionitis and funisitis.\textsuperscript{3,5,43,44} Observing neutrophil migration within placental tissues forms the core of the histological assessment. The histological interpretation of the varying patterns of inflammation in the placenta demonstrates that maternal polymorphonuclear leukocytes form the predominant group of inflammatory cells in the extra-placental membranes and subchorionic fibrin.\textsuperscript{3,5,43,44} Although the majority of such inflammatory cells are maternally derived, with extensive infection an associated fetal inflammatory response will occur, with fetal polymorphonuclear leukocytes forming the predominant group in the infiltrate within the umbilical cord and chorionic plate.\textsuperscript{3} This process has been demonstrated by fluorescence in situ hybridization studies for X and Y chromosomes in pregnancies with male infants.\textsuperscript{45} This histological distinction is often relied on to support differentiation of maternal from fetal inflammatory response.
Figure 1 Photomicrograph demonstrating acute histological chorioamnionitis, with marked infiltration of the fetal membranes by neutrophil polymorphs (H&E, original magnification ×100)

While a definite difference between fetal and maternal inflammatory responses has been fairly conclusively demonstrated histologically, determining the histological extent, if any, of a clinically important inflammatory response remains more difficult. Histological assessment of membranes and cord has been subject to a number of grading systems, usually applied in research settings. The most commonly used system of identifying various reaction patterns of inflammation describes both maternal and fetal inflammatory response in terms of stage and grade, with stage corresponding to degree of progression of inflammation and grade relating to the intensity of the infiltrate. For the cases which formed the basis of this classification, overall interobserver agreement was reasonable, at 80%. In addition, while there is some evidence supporting the association of severe grade inflammation with clinical outcome, the overall clinical significance of this classification system remains untested on a large unselected population. In addition to an accumulation of neutrophils in the fetal membranes and a fetal inflammatory response affecting chorionic plate and umbilical vessels, ascending infection may also be associated with subchorionic intervillositis, with neutrophil collections within the maternal intervillous space immediately below the chorionic plate of the placenta proper, or very rarely, villitis, with inflammation of the chorionic villi. Ascending genital tract
infection may also lead to a localized choriodecidual inflammatory process in the membranes overlying the internal cervical os, without the development of more florid classical chorioamnionitis, but which similarly results in the release of inflammatory mediators and subsequent onset of labour, even without organism colonization of the amniotic cavity.\(^3,4^8\)

The pathway which mediates the association between chorioamnionitis and the development of clinically significant sequelae in the neonate is now fairly well established to be related to a fetal inflammatory response. Many of the studies supporting this concept have examined markers such as interleukin 6 (IL-6) levels in cord blood at delivery (as a marker of fetal immune system activation) in relation to neonatal outcome. Clinical outcomes examined vary considerably amongst different studies but overall there is data that cord blood IL-6 levels are useful both in the research setting and potentially in a clinical setting. Preterm neonates with severe neonatal morbidity have higher plasma IL-6 levels than those with uncomplicated outcomes.\(^4^9\) Employing funisitis/chorionic plate inflammation as a histological marker of a fetal inflammatory response, preterm infants with such a fetal response in the placenta have higher neonatal mortality and morbidity than those without.\(^5^0\) IL-6 levels are also raised in low-risk term labours with no evidence
of intercurrent infection, but these levels are lower than low-risk term labours which have positive histological evidence of inflammation. Intra-amniotic inflammation (using matrix-metalloproteinase 8 as a marker) is associated with increased levels of IL-6 in infants delivered to mothers with preterm premature rupture of membranes, but IL-6 levels are higher again in cord blood where there is evidence of both intra-amniotic inflammation and positive amniotic fluid microbiological cultures. The onset of labour in non-labouring mothers with preterm premature rupture of membranes is more rapid in cases where there is also evidence of a fetal inflammatory response.

**RELATIONSHIP BETWEEN CLINICAL AND LABORATORY DIAGNOSIS OF CHORIOAMNIONITIS**

**Maternal markers**

The specific parameters are well-documented in standard obstetric texts and clinical practice guidelines. In summary, clinical markers include maternal fever, tachycardia, abdominal tenderness, purulent or offensive vaginal discharge, raised maternal white cell count, and fetal tachycardia. Primary culture of high vaginal
swabs and maternal full blood count remain the usual investigations undertaken where there is clinical suspicion of ascending genital tract infection in pregnancy. Specific transport media are recommended for specimen transfer to the microbiology laboratory, sampling with synthetic rather than cotton/wood swabs is recommended, and the transport medium should be inoculated with the swab by the bedside, especially for ureaplasma and mycoplasma detection.22

Data suggest that positive genital tract cultures predict only around 50% of positive amniotic fluid cultures, with a false positive rate of 20–30%. Detecting bacterial 16S ribosomal DNA by PCR is more sensitive in detecting evidence of bacterial infection but this investigation is not established in routine clinical practice.18 Matrix metalloproteinase-8 (neutrophil collagenase) is an enzyme produced by neutrophils as part of an acute inflammatory response. MMP-8 levels are increased in amniotic fluid infection,55 in keeping with the expected neutrophil response. Testing for MMP-8 can be carried out on a qualitative basis by “near patient” bedside testing with a monoclonal antibody based kits.56,57 One recent study has positively correlated a positive MMP-8 test with intra amniotic inflammation and adverse outcome including histologically confirmed chorioamnionitis.58 Fetal fibronectin assays are
commonly undertaken in women presenting with suspected preterm labour between 20 to 34 weeks gestation, with a negative result indicating that delivery within the subsequent two weeks is unlikely. A relationship between positive fetal fibronectin assay and histological evidence of acute placental inflammation at delivery has been sought but no convincing independent association demonstrated.\textsuperscript{59}

Sub-clinical chorioamnionitis refers to the common circumstance where histological chorioamnionitis is recognized following examination of the fetus and placenta, the mother having remained asymptomatic intra-partum.\textsuperscript{60} Specific clinical markers to improve the detection of subclinical chorioamnionitis in preterm infants have been studied and maternal markers which significantly correlate with subclinical infection include elevated maternal white cell count and prolonged PROM.\textsuperscript{61} Histological chorioamnionitis is identified in around half of all cases of preterm premature rupture of membranes, with placental cultures being negative in around one third of these cases, representing deficiencies in the use of bacterial cultures for detection of placental inflammation.\textsuperscript{62} Although associated, there is also poor correlation between histological chorioamnionitis and maternal pyrexia and/or leukocytosis, with these clinical features having a true positive rate for chorioamnionitis of around 60–70\% and a false positive rate of 20–30\%.\textsuperscript{62}

**Fetal/placental markers**

Histological examination of placental membranes and cord is, by definition, the means of establishing the presence or absence of an inflammatory cell infiltrate in these tissues. While tissue based assessment remains the most widespread means of confirming membrane/cord inflammation, alternative methods have been considered. The value of a placental smear test, with rapidly processed smears taken directly from the chorionic plate and the fetal surface of the extra placental membranes has been investigated.\textsuperscript{63} Staining methods are analogous to those used on Pap smear tests, and Gram stains can also be undertaken. Identification of leucocytes and microorganisms is positively correlated both with histological chorioamnionitis and identification of bacterial species on more extended microbiological culture. Historically, frozen section examination of placental tissue, to identify an inflammatory cell population, has also been considered.\textsuperscript{64,65} but this again is not currently routine practice within histopathology departments since the clinical significance remains unproven. Since the inflammatory process may be focal, affecting primarily the membranes overlying the internal os, this area must be sampled for histological examination. The lack of demonstration of histological chorioamnionitis in many cases may be a consequence of suboptimal or random sampling, rather than targeted sampling of the membrane rupture site.\textsuperscript{66}

It should be clarified that, for the context of this article, chorioamnionitis refers to acute, neutrophilic inflammation of the membranes. An unusual variant of chorioamnionitis, characterized by a T-lymphocytic chronic inflammatory infiltrate in the fetal membranes, has also rarely been described (‘chronic chorioamnionitis’), which
is often associated with lymphocytic villitis, and around half of cases are delivered preterm.\textsuperscript{67,68} Amniotic inflammatory markers also appear increased in these cases, suggesting a direct inflammatory effect, but the relationship of chronic chorioamnionitis to infective aetiologies and ascending genital tract infection remains uncertain. This entity is presumed to represent an immunological rather than infective process.\textsuperscript{69}

Clinical assessment and laboratory investigations of the newborn are associated with presence of histological chorioamnionitis, particularly, in preterm infants. Lower gestational age and markers of fetal inflammatory response (including raised IL-6 and CRP levels) are particularly associated with histologic chorioamnionitis.\textsuperscript{58,70}

**Incidence of chorioamnionitis**

The true incidences of chorioamnionitis and funisitis vary according to the population characteristics but for clinical chorioamnionitis, the incidence is reported to be between 0.5\%--10\% of all pregnancies, 1--7\% at term,\textsuperscript{71--73} and 10--20\% of preterm (<33 weeks) deliveries.\textsuperscript{74} When considering histological chorioamnionitis, there is a clear and strong relationship with gestational age, the highest frequency affecting spontaneous miscarriages at 20--24 weeks of gestation (around 80--90\% of cases), falling to around 10\% of deliveries at term.\textsuperscript{75} Interestingly, chorioamnionitis is very rarely the cause of spontaneous first trimester miscarriage.\textsuperscript{75} Histological chorioamnionitis is identified in around 10\% of deliveries at term, around 30\% of all preterm labour with intact membranes,\textsuperscript{76} and around 50\% of those presenting with preterm premature rupture of membranes.\textsuperscript{62} Longer duration of labour is associated with increased frequency of histological chorioamnionitis, being reported in 20--30\% of deliveries following labour compared to <5\% delivering at term with no labour.\textsuperscript{77,78} These data indicate that ascending genital tract infection is a cause of a significant proportion of preterm deliveries, with or without premature rupture of membranes, but can also develop during the process of labour, possibly in relation to procedures such as vaginal examination, digital vaginal examinations in patients with premature rupture of membranes significantly reduce the time to delivery.\textsuperscript{79}

**CLINICAL OUTCOMES ASSOCIATED WITH CHORIOAMNIONITIS**

Evaluating studies reporting on the clinical outcomes of chorioamnionitis is difficult since such studies are predominantly retrospective, histological definitions of chorioamnionitis employed may vary and clinical (maternal) symptoms and signs may be reported as surrogate markers although these are not well correlated with identifiable histological inflammation.\textsuperscript{80} Less well explored, but of importance, is the concept that clinical outcomes are not dependent solely on maternal clinical assessment or placental histology, well-characterized or otherwise, but are highly dependent on subsequent clinical care received. This is likely to be different in more recent studies, making comparison of older and contemporary studies
problematic. The disease process and epidemiology may also be modulated by antenatal treatment received by the mother. An example is the policy for group B streptococcus screening; this is not currently recommended in the United Kingdom but standard practice in the United States.81–83

Maternal complications

Preterm labour accounts for around 10% of all deliveries,84 having multiple well recognized clinical and epidemiological associations,85 amongst which chorioamnionitis is clearly established75,86–88 Early spontaneous preterm births are particularly associated.75,89 Differentiating premature rupture of membranes attributable to primary infection from either preterm labour with intact membranes or preterm rupture due to non-infective causes with subsequent ascending infection may be difficult, and both mechanisms occur.62 Bacteria can adhere to and invade intact membranes90 and production of cytokines by macrophages and other cells mediating the inflammatory response may mediate the initiation of labour.91–93 A small number of studies have examined the question of recurrent preterm birth and placental inflammation. Again, the histological scoring systems used for these studies is variable, and fetal and maternal inflammatory responses have not always been reported separately. Overall, there appears to be some evidence that, for a proportion of women delivering prematurely, the placenta may show inflammatory changes which are followed by a subsequent preterm delivery with, again, a placenta showing significant inflammation.94,95

Overwhelming maternal sepsis is occasionally but consistently reported as a complication of chorioamnionitis. It is a relatively rare occurrence, forming only a small proportion of pregnancy related intensive care admissions and prognosis is generally good with appropriate treatment.96–98 The hypothesis that chorioamnionitis is positively associated with placental abruption in preterm and term birth is recurrent, the premise being that the localized inflammatory processes disrupt the normal placental attachment. A recent study suggested a more specific relationship between abruption at term and severe chorioamnionitis.99 Whilst most cases of abruption are associated with other well-validated epidemiologically derived associations such as previous abruption, hypertension, ethnicity, smoking and cocaine use, an association with chorioamnionitis is now well established.100 In addition to abruption, a large population based study reported that histological chorioamnionitis was also associated with increased rates of septic pelvic thrombophlebitis and maternal pelvic abscess.101

Fetal/Neonatal complications

The reported rates of chorioamnionitis in stillbirth are extremely variable, ranging from 10%–95%.102 Intrauterine death with retention and subsequent delivery of a
macerated fetus is a pathological process distinct from early spontaneous preterm delivery of a fresh stillborn fetus. In the group of preterm non-macerated stillbirths with histological evidence of an established fetal inflammatory response,\textsuperscript{102,103} it is likely that ascending infection caused the pregnancy loss. However this specific group accounts for only around 10% of all stillbirths and conclusions drawn from studies including retained macerated stillbirth, where the interval between recognition of fetal death and delivery may extend over a number of days, are much less clear. Since a fetal inflammatory response requires a living fetus, the identification of a maternal chorioamnionitis in association with delivery of a retained intrauterine death probably represents a secondary process unrelated to the cause of death.\textsuperscript{3}

The most important pathway relating chorioamnionitis to adverse neonatal outcome appears to be the fetal inflammatory response syndrome.\textsuperscript{104} However, initial assessment of the data indicates that overall, histological chorioamnionitis is associated with improved survival in very preterm infants compared to gestational age matched cases with no inflammation, presumably as a consequence of the fact that preterm deliveries associated with ascending infection are otherwise normal infants whereas those delivered preterm for other indications will by definition, have other complications such as fetal growth restriction. Assessing the implications of chorioamnionitis for liveborn infants, born preterm or term, despite confounding factors continues to be problematic.\textsuperscript{105} However, a meta-analysis carried out ten years ago reported a significant association between clinical chorioamnionitis and both cerebral palsy and periventricular leukomalacia in preterm infants, and an association between histologic chorioamnionitis and periventricular leukomalacia in preterm infants. For term infants, there was a positive association between clinical chorioamnionitis and cerebral palsy.\textsuperscript{106} A subsequent extended meta-analysis reported an association between clinical chorioamnionitis and cerebral palsy with a random effects model,\textsuperscript{107} and a more recent meta-analysis reported associations between both clinical and histological chorioamnionitis and cerebral palsy in studies predominantly, but not exclusively, of preterm infants.\textsuperscript{108}

Problems relating to diversity of inclusion criteria and definitions of chorioamnionitis persist in evaluating studies examining endpoints other than cerebral palsy. For preterm infants, in one large recent study of \textless 28 week gestation infants who had cranial ultrasound and review at approximately 2 years, an association between histological inflammation and both ventriculomegaly and cerebral palsy was demonstrated.\textsuperscript{109} Conversely, periventricular leukomalacia has been linked, in preterm infants born at 23–34 weeks of pregnancy, with chronic inflammation in the decidual endometrium but not with histological acute chorioamnionitis.\textsuperscript{110} Also notable is a reported association between mononuclear (chronic inflammatory cell) infiltrates within the decidua and increased risk of intra-ventricular haemorrhage in infants delivered between 23–32 weeks:\textsuperscript{111} although histological inflammation was associated with fetal inflammatory response syndrome and also with necrotizing enterocolitis, there was no link with intraventricular haemorrhage or indeed with neonatal death. A separate study of
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<32/40 gestation neonates identified an association between chorioamnionitis with a histological maternal inflammatory response and intra-ventricular haemorrhage, but no relationship with a histological fetal inflammatory response. However, subanalysis of a range of clinical markers of neonatal wellbeing in preterm infants suggested that histological chorioamnionitis was associated with lower gestational age, higher C reactive protein levels, higher maternal white cell count and a higher rate of preterm prelabour rupture of membranes.61,112

When considering long term outcome in extremely low birth weight infants, histological chorioamnionitis has not been demonstrated to be predictive of poorer outcome, but a severe fetal response was associated with abnormal neurocognitive testing at 8 years of age.113 In term infants, a study reported an association between maternal fever, with or without clinical markers of chorioamnionitis, and neonatal encephalopathy.114 Higher IL-6 levels are present in the cord blood of infants delivered to mothers with clinical signs of chorioamnionitis who required admission to a neonatal intensive care unit, and are also associated with increased risk of encephalopathy and seizures.73

Studies examining the outcomes of (mainly clinical) chorioamnionitis suggest increased risk of neonatal sepsis.115–11 Recent genetic studies have begun to identify fetal polymorphisms in components of the immune response, such as Toll like receptors, interleukin 10 and PLA2G2A, which may affect the predisposition of preterm neonates to sepsis in the setting of clinical chorioamnionitis.115 A recent micro-array study of fetal leucocyte RNA identified increased transcription of genes involved in antigen presentation and processing, immune response and critical cellular metabolism, results similar to those previously described for adult systemic inflammatory response syndrome and sepsis.118

The effects of chorioamnionitis on premature infant lung function appear complex with apparently contradictory findings of decreased frequency of short-term respiratory distress syndrome but increased frequency of lung-term chronic lung disease/bronchopulmonary dysplasia.119 While both maternal and fetal inflammatory responses have been reported as protective for acute respiratory distress syndrome, with a fetal inflammatory response identified as exerting a particularly marked effect,120 others report that there is an impaired response to surfactant treatment in preterm infants with chorioamnionitis, worse in those with a histological fetal response.121 These findings may at least in part explain the increased risk of progression to chronic lung disease thought to exist in ex-premature infants with chorioamnionitis, but it should also be noted that the criteria for a clinical diagnosis of respiratory distress may be quite variable making comparison of studies difficult.122

Neonatal leukaemoid reaction has also been described in low birth weight preterm infants, with very raised neutrophil counts,123–125 attributed to a transient stimulus to neutrophil production by elevated granulocyte colony stimulating factor levels in the first days of life. The presence of histological chorioamnionitis is associated with an increased risk of neonatal leukemoid reaction, and associated increased risk of bronchopulmonary dysplasia development.126
CONCLUSION

In summary, chorioamnionitis represents a reliable marker of ascending genital tract infection and inflammation, which is currently diagnosed based on a ‘gold-standard’ of histological examination of the delivered placenta and membranes. Chorioamnionitis is strongly associated with preterm birth and late second trimester miscarriage and the associated fetal inflammatory response may contribute in some cases to the development of a range of neonatal complications such as cerebral palsy and bronchopulmonary dysplasia. Future research will focus on development of early and reliable clinical markers of an inflammatory response and development of targeted therapies.

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