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Chorioamnionitis: Important Risk Factor or Innocent Bystander for Neonatal Outcome?

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Key Words

Antenatal infection · Prematurity · Bronchopulmonary dysplasia · Respiratory distress syndrome · Cerebral palsy · White matter disease · Periventricular leukomalacia · Small for gestational age · Antenatal steroids

Abstract

Chorioamnionitis as a major risk factor for spontaneous preterm birth, especially at earlier gestational ages, contributes to prematurity-associated mortality and morbidity. A gestation-independent effect of chorioamnionitis on neonatal outcome is much more difficult to assess. The influence of chorioamnionitis on neonatal outcome has become less evident with advances in neonatal care. A short-term beneficial effect of histological, but not clinical chorioamnionitis on incidence and severity of respiratory distress syndrome in preterm infants is evident. This maturational effect is accompanied by a susceptibility of the lung for further postnatal injury, which predisposes for bronchopulmonary dysplasia. Chorioamnionitis is associated with cystic periventricular leukomalacia, intraventricular hemorrhage and cerebral palsy in preterm infants, but its association with noncystic white matter disease is not clear yet. Prenatal inflammation/infection has been shown a risk factor for neonatal sepsis. A single course of antenatal steroids can be regarded safe in clinical as well as histological chorioamnionitis.

Chorioamnionitis

The term chorioamnionitis is used to describe an intrauterine status of inflammation in tissues of either mixed fetal-maternal (choriodecidual space) or fetal origin (chorioamniotic membranes, amniotic fluid and umbilical cord) [1]. Histological chorioamnionitis is accompanied by evidence for invasion of pathogens in normally sterile tissues in most cases [2, 3]. Apart from histological signs (infiltration of polymorphonuclear cells), microbiological (positive culture/polymerase chain reaction for pathogens) and biochemical (elevated intraamniotic cytokines) criteria are often used to define chorioamnionitis [4–6]. Most pathogens associated with chorioamnionitis are of low virulence and the inflammatory process in most cases is a subclinical condition. Clinical chorioamnionitis, variably defined by the presence of maternal fever, tachycardia, leukocytosis or elevated C-reactive protein, uterine tenderness, foul-smelling vaginal discharge or fetal tachycardia, is present only in a minority of cases with either histologically, microbiologically or biochemically proven chorioamnionitis (fig. 1) [1, 7–9].

The fetal inflammatory response syndrome (FIRS) is characterized by activation of the innate immune system of the fetus exposed to infection/inflammation in utero [10]. FIRS was originally defined on the basis of increased cord blood concentrations of interleukin (IL)-6 which

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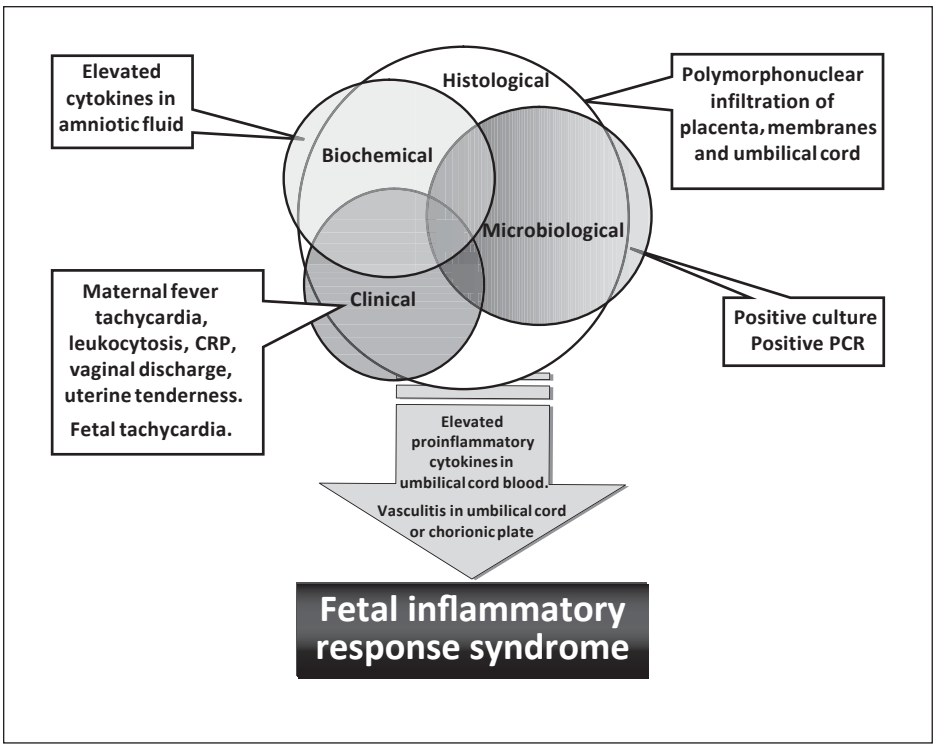

Fig. 1. Schematic illustration of different approaches to define chorioamnionitis and their interrelationship. The most sensitive method to define chorioamnionitis is by histological examination. Clinical signs of chorioamnionitis will be found in a minority of cases with 'microbiological', 'biochemical' or 'histological' chorioamnionitis. An inflammatory response of the fetus is reflected by elevated blood cytokines or vasculitis of the umbilical cord/chorionic plate.

was shown associated with adverse neonatal outcome [11]. Meanwhile, many other soluble blood markers for FIRS, mainly proinflammatory cytokines like IL-1β and tumor necrosis factor-α (TNF-α), have been introduced [10] and histological funisitis/chorionic vasculitis has been suggested as the histological counterpart of FIRS.

Chorioamnionitis and Preterm Birth

In the last decades, advances in perinatology and neonatology have led to a considerable amelioration of neonatal outcome after preterm birth. Meanwhile, the world's birth rate of preterm infants has been consistently rising with prematurity being the most important risk factor for death before the first birthday in high-income countries [12]. Most recently, data from a multicenter study, including more than 1,200 infants born before 28 weeks of gestational age, have clearly underlined the close relationship of microbial colonization of placental tissue as well as histological evidence for placental and umbilical cord vessel inflammation with spontaneous early preterm birth [13, 14]. According to microbiological data, at least every fourth preterm birth is supposed to be caused by intrauterine bacterial infection [12]. An ethnic predisposition for histological chorioamnionitis, which cannot be explained completely by different utilization of prenatal healthcare and lifestyles [15], seems to contribute to the higher prevalence of preterm deliveries among African-American women [16]. The recovery rate of microorganisms with culture techniques both from amniotic fluid and from placental tissues decreases significantly with increasing gestational age in women presenting with preterm labor [17, 18]. Reported colonization rates have been as high as 79% for births at 23 weeks of gestational age in this group [18]. Elevated concentrations of proinflammatory cytokines in amniotic fluid have been shown associated with delivery at lower gestational ages after preterm labor, which suggests that intrauterine infection triggers preterm birth via mechanisms involving local cytokine production [19, 20]. Intraamniotic IL-6 concentrations have been identified as a more valuable predictor of preterm birth than positive amniotic fluid culture results [21]. However, this does not inevitably mean that intrauterine inflammation is often present in the absence of infection. It rather reflects the inadequacy of amniotic fluid cultures to detect pathogens like *Ureaplasma* compared to newer techniques like polymerase chain reaction

Table 1. Studies assessing the association of histological chorioamnionitis with RDS and BPD

Reference (first author)	Cohort	Study type	Group size	Study period	Outcome	
					RDS	BPD
Watterberg, 1996 [36]	<2,000 g n = 53	prospective single-center	36 CA+	1987–1989	↓	↑[a]
Redline, 2002 [34]	<32 weeks' GA <1,500 g, n = 371	retrospective single-center	169 CA+ CA+, CPV+	1995–1997	n.a. n.a.	→ →
Van Marter, 2002 [35]	BW <1,500 g	retrospective multicenter case-control[c]	146 CA+	1991–1993	n.a.	↓[b] ↑[d]
Ogunyemi, 2003 [39]	<32 weeks' GA n = 774	retrospective single-center	254 CA+	1992–2000	→	↑
Kent, 2004 [29]	<30 weeks' GA n = 241	prospective single-center	40 CA+F– 40 CA+F+	1996–2001	n.a. n.a.	→ →
Richardson, 2006 [49]	25–34 weeks' GA n = 606	retrospective single-center	114 CA+F– 178 CA+F+	1995–2003	→ →	→ →
Zanardo, 2008 [38]	<32 weeks' GA n = 287	prospective single-center	68 CA+	2001–2006	→	↑
Kaukola, 2009 [28]	<32 weeks' GA n = 163	prospective single-center	64 CA+	1998–2002	↓	→
Lahra, 2009 [30]	<30 weeks' GA n = 724	retrospective single-center	138 CA+F– 219 CA+F+	1992–2001	↓ ↓	n.a. n.a.
Lahra, 2009 [31]	<30 weeks' GA n = 761	retrospective single-center	140 CA+F– 208 CA+F+	1992–2004	n.a n.a.	→ ↓

GA = Gestational age; CA = histological chorioamnionitis; F = histological funisitis/umbilical cord vasculitis; CPV = chorionic plate vasculitis; n.a. = data not available.

[a] Defined as need for supplemental oxygen on day 30 of life. [b] If mechanically ventilated <7 days. [c] Infants with and without BPD were matched. [d] If mechanically ventilated ≥7 days or postnatal sepsis.

[22]. Physiological labor at term is also characterized by histological chorioamnionitis in a considerable number of cases and by elevated intraamniotic proinflammatory cytokine levels, underlining the crucial role of inflammation in normal parturition [23].

To conclude, there is unequivocal evidence that chorioamnionitis – either defined clinically, histologically, microbiologically or biochemically – is a major risk factor for spontaneous preterm birth [24]. It therefore contributes to the high morbidity and mortality of infants born prematurely [1].

Chorioamnionitis as Gestation-Independent Risk Factor for Neonatal Outcome – Methodological Pitfalls

There is still controversy if gestation-independent effects of chorioamnionitis on neonatal outcome exist [6]. Some cohort studies addressing this issue might simply not have the power to identify gestational age as a confounder or risk modifier. Besides, reported associations between chorioamnionitis and adverse outcome in preterm and term infants largely depend on the criteria that were used to define chorioamnionitis [2, 25–27]. Two broad disease groups have been identified to lead to preterm birth: inflammation and placental dysfunction resulting from vascular malfunction [13]. Since disorders of the latter group are also closely related to neonatal morbidity and mortality, assessment of chorioamnionitis as a risk factor for adverse outcome in very premature infants is hampered by the lack of a 'normal' control group.

Chorioamnionitis and Respiratory Outcome

The association between antenatal infection/inflammation and neonatal respiratory outcome has been extensively addressed in the last two decades with considerably variable results (table 1) [28–39]. Diverging defini-

tions of inclusion criteria and major end points of the studies contribute to these variations [40].

Watterberg et al. [36] introduced the concept that exposure to intrauterine inflammation decreases the likelihood of respiratory distress syndrome (RDS) in premature infants but increases the risk for bronchopulmonary dysplasia (BPD). They demonstrated that histological chorioamnionitis led to adrenal stimulation, resulting in increased cortisol secretion and accelerated lung maturation [41]. In animal models, a maturational effect of prenatal inflammation on the lung has been demonstrated [42, 43]. However, this effect has not been conferred by cortisol [44].

None of the infants in the initial Watterberg study [36] received antenatal steroids, which has meanwhile become standard care in cases of imminent preterm delivery [45]. This approach has been clearly linked with a decreased rate of RDS whereas the incidence of BPD has been shown unaffected [46–48]. The widespread use of antenatal steroids might partially explain why many later studies have shown either decreased or unaffected rates of RDS associated with histological chorioamnionitis but have not demonstrated a significant increase in BPD [2, 29, 31, 40, 49, 50].

In the late 1990s, an association between elevated amniotic fluid concentrations of proinflammatory cytokines and the development of BPD was demonstrated [51, 52]. These data suggested that fetal aspiration of cytokines contributes to a local pulmonary inflammation which makes the lung more susceptible for further injury from barotrauma or oxygen toxicity. In a retrospective study, amniotic fluid concentrations of matrix metalloproteinase-8 and intraamniotic white blood cell counts were higher in infants born with a gestational age $\leq$32 weeks who developed BPD without RDS compared to infants with BPD after RDS [53]. These data imply that intraamniotic inflammation is differentially associated with patterns of respiratory disease in these patients [53]. An increased influx of neutrophils, a higher expression of proinflammatory cytokines and an increased apoptosis of airway epithelial cells has been demonstrated in lung tissues of stillborn fetuses exposed to chorioamnionitis [54, 55].

Elevated IL-6 concentrations in cord blood predicted BPD in infants born <34 weeks of gestation better than elevated intraamniotic IL-6 [37]. These data led to the conclusion that FIRS contained an even more pronounced risk for BPD than local intraamniotic inflammation. They were corroborated by studies linking umbilical cord vasculitis/funisitis, as histological counterparts of FIRS, with BPD [25, 32]. Other studies either did not find any association between chorioamnionitis with funisitis and the development of BPD [29, 49] or even an inverse association [30]. However, for the latter study, data of infants born in a single center over a 13-year period were analyzed, an interval in which practice of neonatal care changed considerably [30].

In a case-control analysis nested in a cohort study, chorioamnionitis with fetal vasculitis was not a better predictor of BPD than isolated chorioamnionitis, which even was associated with a decreased rate of BPD in infants who were ventilated for less than 1 week [35]. However, in this study, chorioamnionitis was associated with an increased risk of BPD if mechanical ventilation had to be sustained for more than 7 days or infants experienced postnatal sepsis. This documented synergy underlines the complex interrelationship between prenatal inflammation and postnatal factors in the pathophysiology of this pulmonary disease (fig. 2) [56–58]. Advances in neonatal care which interfere with these modulating factors, like early administration of exogenous surfactant in combination with continuous positive airway pressure or noninvasive ventilation, will probably further mitigate the role of prenatal inflammation for the development of BPD [59–61].

Clinical chorioamnionitis has been identified as an independent risk factor for RDS in premature infants [62, 63], whereas histological chorioamnionitis seems to confer a beneficial effect on the incidence of RDS [2, 31, 36, 64, 65]. These data for histological chorioamnionitis are consistent with a maturational effect of prenatal exposure to inflammation on lung development shown in an animal model [43]. However, in this model, pulmonary maturation, induced by fetal inflammation, is associated with a significantly disturbed structural development of the lung [66].

Most recently, a cohort study including 301 infants with a gestational age <32 weeks has outlined another interesting effect of prenatal exposure to inflammation on respiratory physiology in infants at risk for RDS and BPD [67]. Histological chorioamnionitis deteriorated the response to exogenous surfactant associated with a longer need for mechanical ventilation in this study. This effect was more prominent in infants who also had histological signs of a fetal inflammatory response. In the group of infants treated with exogenous surfactant, those with a fetal inflammatory response developed BPD more frequently than those without signs of systemic inflammation. These observations underline that chorioamnionitis has synergistic effects with mechanical ventilation on the

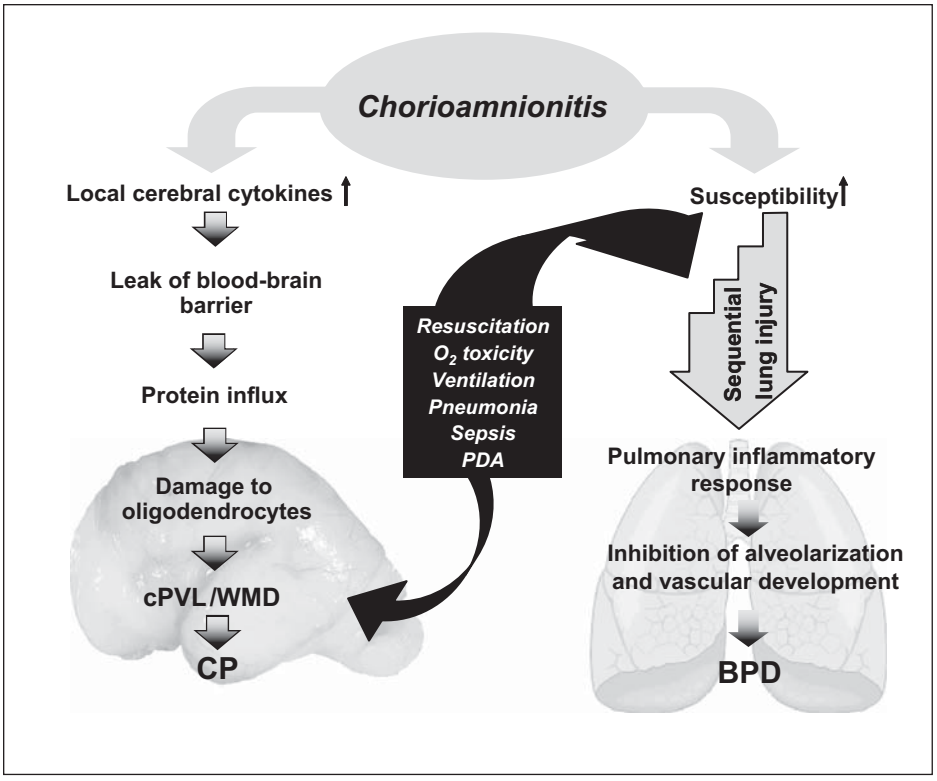

Fig. 2. Potential pathogenic sequences linking exposure of the fetus to prenatal inflammation with subsequent disturbed lung development [56] and cerebral injury [90] under further influence of postnatal factors.

development of BPD [35]. Moreover, they allow the assumption that RDS after preterm birth resulting from chorioamnionitis may be distinct from that after preterm birth due to other reasons [68].

Thus, current evidence suggests that histological chorioamnionitis seems to decrease the risk of RDS in preterm infants through a maturational effect which in turn seems to contribute to a susceptibility of the lung for further postnatal injury (fig. 2) [40].

Chorioamnionitis, Cystic Periventricular Leukomalacia, White Matter Disease and Cerebral Palsy

Cerebral palsy (CP), a nonprogressive impairment of posture and motor function, is a major cause for physical disability in childhood [69]. In very premature infants, CP is clearly associated with cystic periventricular leukomalacia (PVL). Epidemiological studies addressing the risk for cystic PVL and later development of CP after perinatal infection/inflammation have come to variable results. Elevated cytokine levels in amniotic fluid [70, 71] and in cord blood [72–74], indicating FIRS, were described to be related with CP in preterm and term neonates. However, in another study, neonatal blood cytokine levels in infants born before 32 weeks of gestation did only predict cystic PVL but not later CP [75]. Two systemic reviews of case-control and cohort studies have identified both clinical and histological chorioamnionitis to be associated with an increased risk of CP [76, 77]. The earlier meta-analysis also demonstrated an association of both entities with cystic PVL [76].

Other studies suggest that chorioamnionitis might be a risk factor for adverse neurological outcome in more mature infants. A case-control study including 109 children with spastic or dyskinetic CP identified clinical chorioamnionitis as a risk factor for CP in infants born after 36 weeks of gestation [78]. In a cohort of 483 singletons with a mean gestational age of 34.5 weeks (range 24–42) histological chorioamnionitis significantly increased the odds ratio for early abnormal brain sonography findings (increased periventricular echodensity or echolucency, severe intraventricular hemorrhage (IVH), ventriculomegaly) [7].

With advances in neonatal care the incidence of cystic PVL, diagnosed by cranial ultrasound, has decreased in extremely premature infants [79]. With the emergence of magnetic resonance imaging (MRI) noncystic diffuse or focal white matter disease (WMD) has been recognized as the most prevalent form of brain injury associated with adverse neurodevelopmental outcome in these infants [80]. Three recent prospective MRI studies failed to show an association between histological chorioamnionitis and microstructural changes of the brain at term [81–83]. It was neither associated with reduced brain volume at term [82] nor with abnormalities of metabolic or microstructural brain development earlier in postnatal life [83]. However, perinatal infection, reflected by maternal fever or proven neonatal sepsis at birth, predicted white matter abnormalities in a cohort of very premature infants [84].

Chau et al. [83] postulated that early postnatal infection and hypotension requiring intervention were more significant risk factors for early WMD than chorioamnionitis. Histological chorioamnionitis has been shown to increase the risk for arterial hypotension with the need for inotropic support on the first day of life [85]. Thus, chorioamnionitis still might contribute to the susceptibility of extremely premature infants to WMD-associated adverse neurological outcome [86]. However, arterial hypotension is inconsistently associated with cerebral white matter injury in very premature infants, largely depending on definitions applied for the two entities [87–88].

Elevated proinflammatory cytokines in cord blood, reflecting FIRS, have been described to predict early cerebral lesions on MRI scans in premature infants, including WMD [89], whereas they did not predict WMD and adverse neurodevelopmental outcome by the age of 2 years in another prospective study [81].

Most recently, the large multicenter ELGAN (extremely low gestational age newborn) study supplied strong epidemiological evidence for a role of prenatal inflammation in the evolvement of WMD and CP in infants at highest risk for these outcomes [3]. Placental tissue for histological and microbiological assessment could be obtained from more than 1,200 infants born in 1 of 14 participating institutions before 28 weeks of gestation. 899 of them had a neurological examination by the corrected age of approximately 24 months. Histological chorioamnionitis as well as detection of microorganisms from placental tissue predicted ventriculomegaly, detected by cranial ultrasound and diparetic CP at follow-up. Moreover, recovery of microorganisms was also associated with cerebral white matter echolucencies in ultrasound scans [3].

Several findings from human studies and animal models support the concept that a fetal exposure to inflammation triggers a prolonged neuroinflammatory response of the central nervous system affecting the development of brain structure and function [90]. Such a sustained maturational disturbance of the fetal/neonatal brain plays an important role in the pathogenesis of both cystic PVL and WMD, summarized under the newly proposed term 'encephalopathy of prematurity' [91].

Postmortem immunohistochemical studies revealed a higher expression of TNF-α, IL-1β and IL-6 in brain sections of premature infants with PVL compared to brains with no signs of PVL [92, 93]. The difference was particularly noticeable in the early phase of PVL and the expression of the proinflammatory mediators was significantly higher in those PVL infants who had suffered from clinical infection [93]. However, the higher expression of proinflammatory cytokines seems to reflect rather a local synthesis in the brain than the dissemination of the mediators via the bloodstream [93]. Accordingly, intraperitoneal endotoxin administration to pregnant rats induced cerebral production of TNF-α and IL-1β in their offspring [94]. Premature infants with WMD were shown to have higher concentrations of proinflammatory cytokines in their cerebrospinal fluid but there was no correlation between paired plasma and cerebrospinal fluid levels for any of the cytokines under investigation [95]. A genotype variation for IL-6, which enhances expression and activity of the cytokine, has been suggested a risk factor for WMD and severe IVH [96].

In an animal model, FIRS induced a local cerebral inflammatory response with disruption of the blood-brain barrier to proteins during a restricted period of fetal brain development, prior to or at the beginning of myelination [97–99]. A possible link between fetal inflammation and white matter injury might therefore be that both locally produced and systemic cytokines signal alterations of the tight junction structure of brain vessels leading to increased permeability for proteins which damage oligodendrocyte progenitors (fig. 2) [100]. Activated coagulation factors in premature infants with a systemic inflammatory response may also play a pathogenic role for cerebral WMD, not solely via vessel occlusion and ensuing brain ischemia but also by promoting inflammation [101].

To conclude, existing data suggest an association between chorioamnionitis (with and without signs of fetal response), cystic PVL and CP. The impact of chorioamnionitis on noncystic WMD identified in MRI is not as clear yet albeit it could be linked to sonographic signs of diffuse WMD in a recent multicenter study of extremely

premature infants. Experimental data strongly support a role for prenatal inflammation in cerebral white matter injury (fig. 2).

Intraventricular Hemorrhage of the Premature Infant

The association of chorioamnionitis with IVH in premature infants has been addressed in several studies. Most of them suggested histological chorioamnionitis as a risk factor for IVH [7, 81, 102, 103], whereas others did not [2, 104]. Increased concentrations of proinflammatory cytokines in umbilical cord blood as markers of a fetal inflammatory response did not consistently predict further development of IVH [81, 102, 105].

Chorioamnionitis, Neonatal Sepsis and Mortality

In several cohort studies, histological chorioamnionitis was shown to be associated with an increased incidence of either culture-proven or clinically suspected sepsis in very preterm infants [2, 65, 106], one study, however, failed to demonstrate such an association [103]. Neither of the studies could demonstrate an effect of histological chorioamnionitis on neonatal mortality [2, 65, 103]. However, for preterm and term infants showing histological evidence of fetal involvement, a recent epidemiological study suggested an increased risk for both postnatal infection and increased mortality [25]. Another multicenter study with a large cohort of preterm infants linked clinical chorioamnionitis to neonatal sepsis but not death [27].

Chorioamnionitis, Fetal Growth Restriction and Poor Neonatal Growth

A large case-control study revealed an association between histological chorioamnionitis and fetal growth restriction, with the strongest association at earlier gestational ages [107]. The authors speculated that release of cytokines and other vasoactive substances in the setting of intrauterine infection might cause vasospasm and alter blood flow to the fetus. Other studies with far smaller sample sizes do not support this finding [103, 108]. Recently, a significant association of histological chorioamnionitis with poor early postnatal growth could be demonstrated in a cohort of 256 preterm infants [108].

Chorioamnionitis and Antenatal Steroids

Current evidence supports a single course of antenatal steroids to accelerate fetal lung maturation in women at risk for preterm birth [45]. This treatment decreases neonatal mortality, the incidence of RDS, IVH, necrotizing enterocolitis and early-onset sepsis without significant maternal and fetal risks. It is therefore considered a standard treatment for preterm birth [45]. Repetitive courses of antenatal steroids are not justified because of their negative effects on fetal growth and head circumference [109].

There have been concerns that the risk of maternal or fetal infection might be increased with the administration of antenatal steroids in cases with clinical evidence of chorioamnionitis [110]. On the other hand, the combined effects of antenatal steroids and chorioamnionitis with and without fetal involvement on neonatal outcome are largely unknown [40].

According to a recent Cochrane analysis, there is no imminent risk of infection with the application of antenatal steroids for women with preterm premature rupture of membranes [45]. Three cohort studies suggest the same for infants with histological chorioamnionitis [46–48]. Antenatal steroids were shown inconsistently associated with decreased mortality and lower incidence of RDS, IVH, WMD and CP in these infants [46, 48, 111]. However, none of the studies proved a synergistic effect of chorioamnionitis and antenatal steroids on any outcome measure. Remarkably, in two studies, antenatal steroids did not increase the risk for adverse neonatal events after clinical chorioamnionitis [47, 48].

Consequently, the administration of a single course of antenatal steroids seems to be safe in cases of obvious or suspected intrauterine inflammation. The efficacy of this approach has to be proven by randomized trials.

Conclusions

Current evidence underlines the role of chorioamnionitis as a major risk factor for spontaneous preterm birth, especially at earlier gestational ages. Therefore it clearly contributes to prematurity-associated mortality and morbidity. In the last decades there have been many attempts to assess a gestation-independent effect of chorioamnionitis on neonatal outcome with variable results. Shortcomings of many clinical studies have been their retrospective character and a lack of power to identify gestational age or other factors, which confound or mod-

ify detected associations between chorioamnionitis and outcome parameters. Besides, there is great variability in inclusion criteria between studies and in the way chorioamnionitis has been defined. The influence of chorioamnionitis on neonatal and long-term outcome has become less evident with advances in neonatal care. Clinical chorioamnionitis was shown to be associated with an increased risk for RDS whereas a short-term beneficial effect on incidence and severity of RDS could be demonstrated for histological chorioamnionitis. However, this maturational effect on the lung seems to be accompanied by a susceptibility of the organ for further postnatal injury. Existing data support a role of chorioamnionitis for cystic PVL, CP and IVH in preterm infants, but its association with noncystic WMD is not yet as clear. Prenatal inflammation/infection has been shown a risk factor for neonatal sepsis. A single course of antenatal steroids can be considered safe for mother and child in clinical as well as histological chorioamnionitis.

In the future, sufficiently powered studies of cohorts, which should be as homogeneous as possible or at least well-matched case-control studies, may add more evidence than currently available to enlighten the role of chorioamnionitis in neonatal outcome.

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