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Perinatal Infections and Cerebral Palsy

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Infections of the mother, the intrauterine environment, the fetus, and the neonate can cause cerebral palsy through a variety of mechanisms. Each of these processes is reviewed. The recently proposed theory of cytokine-induced white matter brain injury and the systemic inflammatory response syndrome (SIRS) with multiple organ dysfunction syndrome (MODS) is evaluated critically.

Transplacental fetal infections

A myriad of viral, bacterial, and protozoan transplacental infections causes permanent central nervous system (CNS) damage to the fetus. In addition to the classical TORCH infections (toxoplasmosis, rubella, cytomegalovirus [CMV], herpes simplex, syphilis), HIV, varicella-zoster virus, and lymphocytic choriomeningitis virus have been documented to cause neuralgic sequelae, including cerebral palsy. These transplacental, congenital infections may account for as many as 5% to 10% of the cases of cerebral palsy [1]. A comprehensive review of each of these infections is beyond the scope of this article, although toxoplasmosis, CMV, and herpes deserve discussion.

The prevalence of toxoplasmosis infection during pregnancy is approximately 1 per 1000; approximately 3000 infants are born with congenital toxoplasmosis annually in the United States [2]. Antimicrobial treatment of infants who have

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congenital toxoplasmosis during the first year of life dramatically reduces the risk of adverse neurologic outcomes. Before the current treatment regimens were established the risk of seizures, mental retardation, and motor abnormalities were each approximately 75%. After implementation of the current treatment regimens, the risks have been reduced to approximately 30% for each neurodevelopmental handicap [3,4].

Congenital CMV may occur in as many as 1 in 1000 live births [5] and is the most common viral infection that is associated with cerebral palsy [6]. Up to 7% of all cases of cerebral palsy may be attributable to congenital CMV infection [7]. More than 90% of infants who have congenital CMV are asymptomatic at birth, yet approximately 10% to 15% of these asymptomatic infants will demonstrate developmental abnormalities, most commonly sensorineural hearing loss or learning difficulties. Almost no infant who is born with asymptomatic CMV develops cerebral palsy; however, approximately 80% to 90% of the infants who have symptomatic CMV have some form of severe neurologic disability. The presence of chorioretinitis, microcephaly, and early neurologic abnormalities in the newborn period are associated highly with adverse neurodevelopmental outcomes [8]; the risk for cerebral palsy among survivors of symptomatic CMV infection ranges from 12% [9] to 50% [10].

The prevalence of neonatal herpes simplex virus infection has been estimated to be between 1 per 5000 to 1 per 26,000 live born infants, with 400 to 1000 cases occurring annually in the United States [11]. Neonatal herpes simplex infection presents as one of three distinct syndromes: localized (skin, eye, and mouth) infection, CNS involvement, or disseminated disease. If treatment is initiated at the time the infection is localized to the skin, eye, or mouth, mortality and neurodevelopmental morbidity is extremely uncommon [12]. Treatment of infants who had established CNS involvement or disseminated disease reduced mortality [13]; however, as many as 50% of the survivors demonstrate neurodevelopmental abnormalities, including microcephaly, hydranencephaly, porencephalic cysts, blindness, learning disabilities, and cerebral palsy [12].

Maternal colonization and infection

Maternal colonization and infection can result in cerebral palsy by causing preterm birth, by causing overwhelming sepsis in the fetus or newborn, or by causing placental insufficiency and birth asphyxia. Recently, it also was proposed that proinflammatory cytokines may cause fetal white matter injury directly. Each of these processes is reviewed.

Maternal infections and preterm birth

Approximately half of all cases of cerebral palsy occur in preterm infants [14]. Accordingly, any condition that increases the incidence of prematurity is expected to increase the incidence of cerebral palsy. There is strong evidence

that maternal infection and inflammation is a common cause of preterm birth. Approximately 25% of all preterm births are associated with maternal infections, and the risk increases as gestation decreases [15,16]. At 23 to 26 weeks' gestation as many as 45% of women in preterm labor have positive amniotic fluid cultures [16]. Undoubtedly, maternal infections are the cause of a substantial number of cases of cerebral palsy based solely upon their impact on the rate of prematurity.

Intra-amniotic infections

Intra-amniotic infections (IAIs; also referred to as "clinical chorioamnionitis" and sometimes simply as "chorioamnionitis") are symptomatic maternal infections that are diagnosed by a combination of maternal fever, leukocytosis, maternal tachycardia, fetal tachycardia, uterine tenderness, and foul odor of the amniotic fluid [17]. IAIs occur in 50% of preterm births that occur before 30 weeks' gestation [18]. Although one may expect to find histologic chorioamnionitis associated with IAIs, Smulian and colleagues [19] reviewed 139 pregnancies with a diagnosis of clinical chorioamnionitis, and found evidence of histologic chorioamnionitis in only 62% of the cases. It is possible that some patients who are diagnosed with clinical chorioamnionitis are exhibiting clinical symptoms that are due to noninfectious processes, such as epidural anesthesia or placental abruption.

There is a strong association between IAIs, preterm rupture of the fetal membranes, and preterm birth. As early as 1950 Knox and Hoerner [20] concluded that "infection in the female reproductive tract can cause premature rupture of the membranes and induce premature labor." IAI is present in 40% of women who are admitted with contractions and preterm, premature rupture of the membranes (PPROMs), and in 75% of women who start labor after admission for PPROMs [17]. Among women who have PPROMs, the likelihood of IAI increases as gestation decreases [18]. Thus, IAI not only increases the risk for preterm births, but increases the risk most dramatically in the extremely preterm births, those who are at the highest risk for neurodevelopmental disabilities.

The detailed mechanisms by which IAIs cause preterm labor are complex, incompletely understood, and beyond the scope of this article; however, it is known that IAIs initiate an immune response that results in an increased production of cytokines, prostaglandins, and metalloproteinases. These products then cause cervical softening, rupture of the fetal membranes, uterine contractions, and ultimately, preterm birth [21,22].

Not only does IAI result in increased preterm births, but preterm infants who are born following IAIs have more complicated courses than do preterm infants who were born without IAIs. Dammann and Leviton [23,24] found an increased risk for intraventricular hemorrhage and white matter disease in preterm infants who were born following IAIs. Zupan and associates [25] found an increased risk for periventricular leukomalacia (PVL) associated with premature rupture of the fetal membranes and IAIs. Perlman and colleagues [26] found that cystic PVL was associated with two risk factors—prolonged rupture of the fetal membranes (odds ratio, 6.6) and IAI (odds ratio, 6.8). Alexander and colleagues [27] found

an increased risk for intraventricular hemorrhage, PVL, and seizures (odds ratio, 2.8, 3.4, and 2.9, respectively) in preterm infants who were born following IAIs. In a recent meta-analysis, Wu and Colford [28] found a relative risk of 1.9 for cerebral palsy in preterm newborns who were born following IAIs.

Histologic chorioamnionitis without intra-amniotic infection

Histologic chorioamnionitis may occur without signs and symptoms of IAI, but with histologic inflammation of the placental (placentitis) or fetal membranes (chorioamnionitis). Although histologic chorioamnionitis theoretically is a nonspecific maternal response to a variety of stimuli, most cases are associated with infections. Micro-organisms have been isolated in approximately 75% of placentas that show evidence of histologic chorioamnionitis [19,29–32]. These studies may underestimate the incidence of infection because of the suboptimal microbiological culture techniques for fastidious organisms, such as *Mycoplasma* spp, or because of the administration of intrapartum antibiotics [33].

Surprisingly, few women who have histologic chorioamnionitis develop clinical findings of IAI. Of all women who have histologic chorioamnionitis or with bacteria documented in the fetal membranes, only 5% to 10% demonstrate findings of IAI [34]. Still, histologic chorioamnionitis without IAI is associated with preterm birth. Hillier and colleagues [35] found that premature delivery was related to the recovery of organisms from the fetal membranes (odds ratio, 3.8) and to the presence of histologic chorioamnionitis (odds ratio, 5.0). The proportion of placentas with evidence of infection was highest among those who delivered at the lowest gestational age.

Preterm infants who are born following histologic chorioamnionitis have an increased risk for intraventricular hemorrhage [36–38], periventricular echodensities [38], PVL [28], and cerebral palsy [39]. In Wu and Colford's [28] meta-analysis, the relative risk of cerebral palsy associated with histologic chorioamnionitis was 1.6, although this finding did not reach statistical significance.

Microbial invasion of the amniotic cavity without rupture of the fetal membranes

IAI and histologic chorioamnionitis usually occur following rupture of the fetal membranes [40]; however rupture of the membranes is not a prerequisite for infection of the amniotic cavity. Romero and Chaiworapongsa [41] reviewed 33 studies and concluded that approximately 13% of women in preterm labor with intact membranes had positive amniotic fluid cultures. The most common organisms that are found in the amniotic fluid of women with intact membranes are *Ureaplasma urealyticum*, *Fusobacterium* sp, and *Mycoplasma hominis* [42]. The women with positive amniotic fluid cultures, intact fetal membranes, and preterm labor usually do not develop clinical findings of IAI. When compared with women with negative cultures, they are more likely to develop IAIs (37% versus 9%), be refractory to tocolysis (85% versus 16%), and have spontaneous rupture of the fetal membranes (40% versus 4%) [43].

Bacterial vaginosis

Bacterial vaginosis is caused by an alteration of the normal vaginal flora and is associated strongly with an increased risk for preterm birth [43–46]. Bacterial vaginosis may occur in up to 20% of all pregnancies and carries a twofold to sixfold increased risk for preterm birth [45,47]. Additionally, there is a strong association between the presence of bacterial vaginosis and the subsequent development of chorioamnionitis [48–50].

Goldenberg and colleagues [22] recently estimated that bacterial vaginosis was responsible for 80,000 preterm births annually in the United States. Approximately 4000 of these infants suffer permanent neurologic disabilities, which suggests that bacterial vaginosis is one of the more common causes of cerebral palsy. Randomized controlled trials have shown inconsistent degrees of effectiveness of antibiotics in the treatment of bacterial vaginosis and the prevention of preterm births [51,52].

Nongenital tract infections

Nongenital tract infections also increase the risk for premature births. A meta-analysis by Romero and colleagues [53] found a strong association between urinary tract infections and preterm birth. Other serious maternal infections, including appendicitis and pneumonia [22], increase the risk for preterm birth but are uncommon in the United States today. Maternal periodontal disease probably is the most common nongenital infection that causes prematurity [54]. The births of as many as 18% of all preterm low birth weight infants may be attributable to periodontal disease [55]. Three recent studies suggested that treatment of periodontal disease during the pregnancy could reduce preterm births substantially, and presumably reduce the incidence of the associated neurodevelopmental sequelae [56–58].

Intra-amniotic infection and cytokine-induced brain damage in the preterm newborn

A substantial mass of evidence has accumulated to support the hypothesis that intrauterine infection with a fetal inflammatory response results in production of proinflammatory cytokines, and that these cytokines disrupt oligodendrocyte development in the preterm fetal brain [59–61]. This leads to reduced myelination, white matter injury, PVL, and ultimately, cerebral palsy. Dammann and Leviton [62,63] proposed development of clinical strategies to modify this cytokine-induced white matter injury.

Laboratory evidence supports the possibility of direct cytokine-induced white matter injury [61,63]. Cytokines can have a direct toxic effect by increasing production of nitric oxide synthase, cyclooxygenase, free radicals, and excitatory amino acid release [64,65]. Intraperitoneal injections of cytokines in various animal models produced astrogliosis and white matter encephalomyelitis [66].

Clinical evidence from newborns supports the hypothesis that an inflammatory-induced cytokine release is directly responsible for a significant proportion of

white matter damage in small preterm infants. An increased risk for brain injury is associated with elevated cytokine levels. Yoon and colleagues found a fourfold to sixfold increased risk for brain white matter damages associated with elevated interleukin (IL)-1β from amniotic fluid [66] and from umbilical cord blood [67]. Yoon and colleagues [68] performed immunohistochemical staining for cytokines from brain sections of 17 infants who had documented PVL and 17 controls who did not have PVL. Cytokines were documented in 88% of the specimens from infants who had PVL, but in only 18% of the infants who did not have PVL. Yoon and colleagues also found a sixfold risk for cerebral palsy among preterm infants who were born with evidence of a fetal inflammatory response (funisitis) [69] or with elevated amniotic cytokine levels [70].

Finally, it is important to remember that not all cases of PVL in the small preterm neonate are from cytokine-induced damage. Hypocarbia [71] and hypotension [72] that are unrelated to infection also have been implicated as causes of PVL, presumably by reducing cerebral blood flow, which thereby, causes brain ischemia.

Maternal infections and cerebral palsy in the term newborn

There is an increased risk for cerebral palsy in term infants who are born following maternal infection. Grether and Nelson [73] found evidence of maternal infection in 37% of term newborns that developed spastic quadriplegic cerebral palsy, but in only 3% of control term infants. Neufeld and colleagues [74] found a twofold risk for cerebral palsy in term infants who were born after maternal infection. Wu and associates [75] reported that chorioamnionitis at 36 weeks' gestation or longer was associated with a fourfold increased risk for cerebral palsy. Wu and Colford's [28] meta-analysis found that among full-term infants, there was a positive association between clinical chorioamnionitis and cerebral palsy with a relative risk of 4.7.

Although studies consistently indicate an association between maternal infection at term and cerebral palsy, there are different pathophysiologic mechanisms by which the infection causes brain injury. The fetus or newborn may be born infected and suffer septic shock, meningitis, or pneumonia with pulmonary hypertension. The fetus may be born asphyxiated after placental dysfunction, and theoretically, the proinflammatory cytokines may cause brain damage directly, as in the preterm newborn.

Neonatal sepsis following maternal colonization and infection

Since its emergence in the 1970s, group B beta streptococcus (GBS) is the most common bacteria that causes early-onset neonatal sepsis. The rate of GBS colonization in pregnant women usually was found to be 15% to 25%. The neonate can acquire the organism from his or her GBS-colonized mother through vertical transmission from the lower genital tract or from acquisition during

passage through the birth canal. If intrapartum antibiotics are not given, approximately 50% of newborns become colonized with GBS [76]; however, neonatal sepsis develops in only 1% to 3% of colonized newborns [77]. The risk factors that predispose a neonate to become infected are prematurity [78], lack of maternal anti-GBS IgG protection [79], prolonged rupture of the fetal membranes, and a high inoculum of the organism in the maternal anogenital tract.

The prevalence of neonatal GBS was approximately 1.4 per 1000 live births before the widespread acceptance of intrapartum antibiotics for the prevention of early-onset GBS sepsis [80]. Over the past 15 years, however, through the efforts of the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the American College of Obstetricians, guidelines have been established for antenatal screening for GBS and intrapartum antibiotic therapy [81]. With the widespread implementation of these protocols, the incidence of early-onset GBS infection has declined by more than 80% [82]. Neonatal mortality from early-onset sepsis has decreased from 25 per 100,000 live births in 1985 to 1991 to 15 per 100,000 live births in 1995 to 1998 [83]. There are no data available to demonstrate a similar decrease in the incidence of cerebral palsy among the survivors of early-onset GBS infection, although such a decrease should be expected. With current management strategies, neonatal GBS infection is a rare cause of cerebral palsy.

Intra-amniotic infection, chorioamnionitis, placental dysfunction, and birth asphyxia

IAI is the most common antecedent to birth depression, low Apgar scores, and neonatal hypoxic-ischemic encephalopathy in term newborns [73,84–86]. IAI and chorioamnionitis have been associated with an increased risk for neonatal seizures, meconium aspiration syndrome, multiorgan dysfunction, neonatal encephalopathy, and a clinical diagnosis of hypoxic-ischemic encephalopathy [86].

Maberry and colleagues [87] compared the course of 123 newborns who were exposed to IAI with 6769 newborns who were not exposed to IAI. The infants who were born following IAI were significantly more likely to have low 1-minute (20% versus 5%) and 5-minute (3% versus 1%) Apgar scores. Although more infants who were born after IAI were acidemic (15% versus 10%), the result did not reach statistical significance.

Grether and Nelson [73] compared 46 children of normal birth weight who had disabling, unexplained spastic cerebral palsy with 378 randomly selected control infants. The children who had spastic cerebral palsy were more likely to have been exposed to a maternal temperature that exceeded 38°C in labor (odds ratio, 9.3) as well as a clinical diagnosis of chorioamnionitis (odds ratio, 9.3). One or more indicators of maternal infection were found in 22% of the children who had cerebral palsy, but in only 3% of the controls. Grether and Nelson estimated that maternal infection might account for 12% of all cases of spastic cerebral palsy, 19% of cases of unexplained cerebral palsy, and 35% of cases

of unexplained spastic quadriplegia. Most of the infants who developed cerebral palsy following maternal infection had signs that were consistent with birth asphyxia; these infants had a significant increase in the need for medication to maintain blood pressure, intubation in the delivery room, neonatal seizures (without meningitis), and a diagnosis of hypoxic-ischemic encephalopathy. Ninety percent of the children who had cerebral palsy following maternal infection had one or more of these findings, and 88% had a 5-minute Apgar score of 5 or less. These data are consistent with the authors' belief that the most likely mechanism for maternal infection to cause cerebral palsy in the term infant is by causing placental dysfunction and birth asphyxia.

Numerous mechanisms have been proposed to explain the occurrence of birth asphyxia in infants who are born after IAI. Chorioamnionitis results in increased cytokine and prostaglandin production. With prolonged chorioamnionitis the concentrations of toxins and cytokines increase, myometrial function is impaired, and labor abnormalities develop. Maternal hemorrhage, an increased need for oxytocin and cesarean delivery, uterine atony, and an increased incidence of first- and second-stage labor abnormalities are all more frequent in women who have IAIs [33,88–90]. In a large, prospective, multicentered trial, uterine atony, 5-minute Apgar score of 3 or less, and neonatal mechanical ventilation within 24 hours of birth were associated significantly with increased duration of IAI [91].

Several mechanisms have been proposed to explain the occurrence of birth asphyxia following IAI. These include placental dysfunction that is due to villous edema [92], placental abruption [90,91], an increase in oxygen consumption that is due to maternal hyperthermia [33], and a primary endotoxic effect upon the fetus [33]. In a study of pregnant sheep, maternal hyperthermia with subsequent hyperventilation and respiratory alkalosis led to a 53% reduction in uterine blood flow, a 30% reduction in umbilical blood flow, and the onset of fetal acidosis [93].

Combined exposure to infection and intrapartum asphyxia may exert a synergistic harmful effect upon the fetal brain [94]. Neonates who are exposed to infection in utero who also had potentially asphyxiating obstetric complications are at a much higher risk for cerebral palsy than are those with only one or no other risk factor [95,96]. Nelson and Grether [97] found that combined exposure to infection and intrapartum hypoxia dramatically increased the risk for spastic cerebral palsy (odds ratio, 78) compared with hypoxia alone. The mechanism for this synergistic effect has not been determined.

Intra-amniotic infection and cytokine-induced brain damage in the term newborn

Shalak and colleagues [98] determined cord blood cytokine levels in 61 term infants who were exposed to chorioamnionitis and admitted to a neonatal ICU and compared the values with those of 50 healthy term infants. Cord cytokine (IL-6, IL 8, and RANTES) levels were higher in infants who were born with

chorioamnionitis. Infants who were born following chorioamnionitis and who had hypoxic-ischemic encephalopathy had significantly higher cytokine levels than did those who were exposed to chorioamnionitis but not hypoxic-ischemic encephalopathy. Long-term follow-up was not provided; however, if the proinflammatory cytokines are harmful to the term neonatal brain, then it would be expected that those who had the highest cytokine levels (ie, those who had chorioamnionitis and hypoxic-ischemic encephalopathy) would be at the greatest risk for brain injury.

Nelson and colleagues [99] examined the stored blood from 31 neonates (25 of whom were term) who had spastic cerebral palsy and from 65 controls. The infants who had cerebral palsy had statistically increased levels of IL-1, IL-8, IL-9, tumor necrosis factor-α, and RANTES. The infants who had elevated cytokine levels and spastic cerebral palsy also had lower Apgar scores, and proinflammatory cytokines are known to increase following hypoxia-ischemia [100,101]; infants with the most severe stages of asphyxia have the highest levels of IL-6 in the cerebrospinal fluid [102]. It remains possible that many of the infants in Nelson and colleagues' [99] study were asphyxiated at birth, and the birth asphyxia caused the cerebral palsy; the elevated cytokine levels were only a marker of the IAI, the birth asphyxia, or both. Further studies of term infants without evidence of birth asphyxia but with elevated cytokine levels should help to clarify this. Insufficient evidence exists to conclude that direct cytokine-induced brain injury occurs in the term and near-term neonate.

Neonatal infections

A variety of neonatal viral, bacterial, protozoan, and fungal infections is known to cause cerebral palsy. The damage may occur because of a direct effect of the infection (eg, meningitis or persistent pulmonary hypertension [PPHN]) or as a result of a systemic inflammatory response that causes shock and multisystem failure.

Early-onset bacterial infections

Pneumonia

PPHN with severe hypoxemia is a common complication of neonatal pneumonia. This tends to be one of the more severe forms of PPHN because of the release of vasoactive substance. In infants who have PPHN that is due to pneumonia, initially there is severe arterial spasm without changes in the morphometry of the pulmonary vasculature [103–105]; changes probably are mediated by the prostaglandin thromboxane A_2 [106,107]. This is followed by increased capillary permeability with increased lung fluid content. The increased capillary permeability is believed to be due to bacterial endotoxins that sequester white

blood cells in the lungs where they release vasoactive agents, such as tumor necrosis factor [105,108]. Treatment of PPHN that is associated with sepsis is extremely difficult because of the hypotension and coagulation disturbances that are associated with overwhelming sepsis [109]; 30% to 40% of the survivors have permanent brain injury, most notably cerebral palsy [109]. Because of the low incidence of GBS pneumonia today, pneumonia with PPHN is an uncommon cause of cerebral palsy.

Meningitis

Meningitis complicates 5% to 20% of the cases of early-onset neonatal sepsis [110]. CNS damage follows as a result of intense inflammatory vasculitis that results in small or large vessel obstruction and infarctions. Following the infarctions bacteria invade the brain and produce necrotizing lesions, which is followed by liquefaction and cavitation [111]. Additionally, an adhesive arachnoiditis leads to a rapidly progressive hydrocephalus in approximately one third of the cases [112]. The associated cardiorespiratory instability of the coincident sepsis and shock can cause additional brain injury. Ultimately, severe encephalopathic damage occurs that results in diffuse cerebral atrophy [111].

Older data suggested that infants who had GBS infection had better outcomes than did those who were infected with gram-negative meningitis [113,114]; however, more recent data demonstrate that the outcome of early-onset GBS meningitis is comparable to the outcome of gram-negative meningitis [115]. Infants who have early-onset GBS meningitis have worse outcomes than do infants who have late-onset GBS meningitis [116]. Other factors that are associated with worse outcomes include the presence of septic shock, coma, neutropenia, seizures, a very high cerebral spinal fluid protein content, and parenchymal injury on CT or MRI [10,115].

CNS damage, including cerebral palsy, is present in 20% to 50% of the survivors of neonatal meningitis [117,118]. In 1977, Haslam and associates [119] reported major neurologic sequelae in 2 of 15 survivors of GBS meningitis. In a prospective assessment of 20 survivors of GBS meningitis from 1974 to 1982, major handicaps were found in 15%, mild cognitive impairments were present in 15%, and 70% were functioning normally [120]. A third study from the 1970s found that following neonatal meningitis, 29% of 6-year-old children had severe sequelae, 21% had mild to moderate sequelae, and 50% were functioning normally [121]. Wald and colleagues [122] reported on 74 patients who had early- or late-onset GBS meningitis; 12% had major neurologic sequelae. As with pneumonia, this is an uncommon cause of cerebral today.

Infected preterm newborns

Infected preterm newborns are at a higher risk for cerebral palsy than are preterm newborns who escape infection. Wheater and Rennie [123] studied 508 very low–birth weight newborns. Of 389 who did not experience neonatal

sepsis, 31 (8%) developed cerebral palsy. Of 119 who experienced neonatal sepsis, 38 (32%) developed cerebral palsy (odds ratio, 4.0). Murphy and colleagues [124] also found that neonatal sepsis increased the risk for cerebral palsy in infants who were born at less than 32 weeks' gestation (odds ratio, 3.6).

Systemic inflammatory response syndrome, sepsis, septic shock, and multiple organ dysfunction syndrome

Infections progress along a continuum of inflammatory reactions from the SIRS to sepsis, severe sepsis, septic shock, MODS, and death [125]. The signs of SIRS can be subtle and consist of only vital sign instability and white blood cell changes. The advanced signs of inflammation—MODS—include metabolic acidosis, shock, renal failure, cardiac dysfunction, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), and CNS disturbances.

The progression of sepsis [126] starts with a release of the proinflammatory cytokines. The body then regulates the inflammation with a release of anti-inflammatory cytokines and cytokine inhibitors. The progression of disease and clinical symptoms is dependant upon an intricate, and only partially understood, balance between the proinflammatory and anti-inflammatory factors. The cytokines and their secondary mediators, including nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins, and complement, cause activation of the coagulation cascade, the complement cascade, and the production of prostaglandins and leukotrienes. Clots lodge in the blood vessels and lower perfusion of the organs. In time the activation of the coagulation cascade depletes the patient's ability to clot, which results in DIC and ARDS. The cumulative effect of this cascade is an unbalanced state with inflammation dominant over anti-inflammation, and coagulation dominant over fibrinolysis. Microvascular thrombosis, hypoperfusion, ischemia, and tissue injury result. Severe sepsis, shock, and multiple organ dysfunction and failure follow, which often lead to death. The survivors are at a increased risk for cerebral palsy that is due to cerebral ischemia.

SIRS and MODS are nonspecific inflammatory reactions and are not confined to patients who have infections. Although asphyxia, trauma, hemorrhagic shock, burns, pancreatitis, malignancies, and autoimmune disorders each can cause a release of the proinflammatory cytokines and result in SIRS and MODS, infections and asphyxia are by far the most common causes in neonates.

With MODS as the common end point of inflammatory symptoms, the MODS of asphyxia can be difficult to distinguish from the MODS of sepsis. Both conditions may follow fetal distress, be associated with low Apgar scores and metabolic acidosis, and demonstrate hypo- or hyperglycemia, thrombocytopenia, DIC, elevated nucleated red blood cells [127], neutrophilia, bandemia, renal dysfunction or failure, cardiac dysfunction or failure, respiratory dysfunction or failure, and CNS dysfunction. Therefore, it often becomes a challenge for clini-

cians to differentiate SIRS and MODS of asphyxia from SIRS and MODS of sepsis. Certain clues may help differentiate the initiating processes:

- The ''gold standard'' for differentiating infectious SIRS and MODS from noninfections causes is a positive culture; however, cultures may produce false-negative results if the mother or infant received antibiotics before collection of the cultures. Slow-growing or fastidious bacteria and virus may be difficult to isolate by culture. Bacterial autolysis [128] and inadequate sample size also can result in false-negative blood cultures.
- Maternal risks factors that are associated with neonatal sepsis include untreated GBS, prolonged rupture of the fetal membranes, IAI, urinary tract infection, and fever; however chorioamnionitis can cause placenta dysfunction that results in asphyxia and asphyxial MODS. Therefore, the presence of maternal risk factors does not necessarily indicate that neonatal MODS was only of an infectious cause.
- Neonatal leukopenia and neutropenia are more likely to be the result of an infection. Leukocytosis, neutrophilia, and bandemia are seen with infectious and noninfectious SIRS and MODS.
- Spinal fluid pleocytosis indicates infection.
- A sentinel event, such as a cord prolapse or ruptured uterus, is indicative of asphyxia.
- Infants who are born severely depressed from infectious MODS are difficult to resuscitate and stabilize. Their mortality within hours of birth is high. Infants who are born with asphyxial MODS are more likely to be resuscitated and stabilized, albeit in a critical condition. They are more likely to survive, although they have a substantial risk for brain damage.
- Recent investigations reported that sophisticated heart rate pattern analysis may differentiate infectious SIRS from noninfectious SIRS [129–131].
- Several laboratory markers of inflammation, including many of the cytokines, have been studied to differentiate infectious from noninfections SIRS and MODS. Of these, procalcitonin and C-reactive protein levels seem to hold the most promise in diagnosing infection [132–134].

Summary

Although there are many mechanism by which maternal, intrauterine, fetal, or neonatal infections can result in cerebral palsy, the mechanisms with the strongest evidence and greatest frequency are the transplacental (TORCH) infections, maternal infections that cause preterm birth (IAI, histologic chorioamnionitis, bacterial vaginosis, and periodontal disease), and birth asphyxia following IAI and placental dysfunction (Table 1). IAI can result in the release of proinflammatory cytokines that cause white matter injury in the preterm infant, but scant evidence exists for such a process in term newborns. Infectious MODS can be difficult to differentiate from asphyxia MODS, and it is common for the two

Table 1
Infectious mechanisms in the etiology of cerebral palsy

Mechanism	Strength of evidence	Relative incidence
TORCH infections cause brain damage	++++	++++
IAI causes prematurity	++++	++
Histologic chorioamnionitis causes prematurity	++	+++
Preterm infants born after IAI or histologic chorioamnionitis have worse outcomes than those not exposed to infection	+++	++
Bacterial vaginosis causes prematurity	+++	++++
Maternal nongenital infections (eg, pneumonia) cause prematurity	++	+
Maternal periodontal infections cause prematurity	++	+++
IAI causes cytokine-induced brain damage in preterm neonates	+++	++
Maternal GBS colonization causes neonatal sepsis	++++	+
IAI causes placental insufficiency and birth asphyxia	+++	++
Synergistic brain damage occurs with IAI and asphyxia	++	++
IAI causes cytokine-induced brain damage in term neonates	+	+
Neonatal pneumonia with PPHN causes hypoxic brain damage	++++	+
Neonatal meningitis causes brain damage	++++	+
Fetal inflammation causes MODS and brain injury independent of asphyxia	++	+

processes to coexist. Infants who are born after exposure to infection and asphyxia have worse outcomes than do infants who are born after only one or other of the two processes.

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