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## Infections and Brain Development

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### Abstract

Several different bodies of evidence support a link between infection and altered brain development. Maternal infections, such as influenza and human immunodeficiency virus, have been linked to the development of autism spectrum disorders, differences in cognitive test scores, and bipolar disorder; an association that has been shown in both epidemiologic and retrospective studies. Several viral, bacterial, and parasitic illnesses are associated with alterations in fetal brain structural anomalies including brain calcifications and hydrocephalus. The process of infection can activate inflammatory pathways causing the release of various proinflammatory biomarkers and histological changes consistent with an infectious intrauterine environment (chorioamnionitis) or umbilical cord (funisitis). Elevations in inflammatory cytokines are correlated with cerebral palsy, schizophrenias, and autism. Animal studies indicate that the balance of proinflammatory and anti-inflammatory cytokines is critical to the effect prenatal inflammation plays in neurodevelopment. Finally, chorioamnionitis is associated with cerebral palsy and other abnormal neurodevelopmental outcomes. In conclusion, a plethora of evidence supports, albeit with various degrees of certainty, the theory that maternal infection and inflammation that occur during critical periods of fetal development could theoretically alter brain structure and function in a time-sensitive manner.

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The development and maturation of the human brain occur throughout the fetal period and is modulated by a set of complex interactions among various signaling receptors, genetic/epigenetic factors, and environmental influences. The principal stages of development during the gestational period are as follows: primary neurulation (weeks 3–4), prosencephalic development (months 2–3), neuronal proliferation (months 3–4), neuronal migration (months 3–5), neuronal organization (5 months postnatal period), and myelination. Myelination of the human brain begins in the second trimester in utero and continues postnatally into adulthood with the fastest growth occurring in the immediate neonatal period. Anomalous development in any of the aforementioned stages can result in

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cerebral pathology. For example, abnormalities in primary neurulation can result in neural tube defects, whereas abnormalities of neuronal organization can lead to mental retardation. Therefore, not only the location but also the timing of the insult have an important role in cerebral development and, ultimately, function. The effects of such prenatal insults underlie some cognitive, behavioral, and psychiatric disorders. The primary goal of this article is to examine the role that infection and inflammation play in fetal brain damage and alteration in neurocognitive function later in life.

Several different bodies of evidence support a link between infection and altered brain development in both animal and human models. This review summarizes existing data. Specifically, we first review examples of associations observed between human maternal illnesses during pregnancy and neurobehavioral and psychological sequelae observed in neonates. We then discuss the relationship between cytokine responses to infection and brain disease. Next, we describe the associations between evidence of placental inflammation, chorioamnionitis, and brain development. Within these latter sections, both human and animal model data are discussed. Table 1 shows the infectious agents that can affect fetal brain development correlated with fetal findings and possible long-term effects as supported by the literature, some of which is reviewed in the following sections. Finally, clinical implications are briefly discussed.

## **SYSTEMIC ILLNESSES DURING PREGNANCY AND PSYCHIATRIC DISEASE: EVIDENCE IN HUMANS**

### **Nonspecific Maternal Infections and Autism Spectrum Disorders**

Multiple epidemiologic and retrospective studies have demonstrated an association between maternal infections, generally defined, and the development of cognitive and psychiatric disease in offspring.

Despite the substantial public health focus on autism, few in the scientific community realize its possible origins in intrauterine infection (IUI), although existing evidence is weak. In a study of the Danish Medical Birth Register from January 1980 through December 2005, more than 1.6 million births were tracked for maternal antenatal admission for an infectious disease. These admissions were then cross referenced for the development of autism through the Danish Psychiatric Central Register. Within the birth cohort, 21,266 mothers (0.7%) were admitted for some type of infection, and 156 of the neonates born to those mothers were diagnosed with autism spectrum disorders (ASDs) on psychiatric follow-up. While no overall association between admissions for antenatal infection and development of ASDs was reported, a subgroup analysis found a significant association between second-trimester antenatal admission for bacterial infection and subsequent development of ASDs (hazard ratio, 1.42).<sup>2</sup> This study is particularly useful in that it followed a large number of patients and reported on diagnoses made by trained physicians, theoretically adding objectivity to the reporting of exposure and outcomes in this cohort. Despite this link, in a follow-up study, the same group studied 96,736 live births in Denmark between 1996 and 2002 and found no association between self-reported common infections during pregnancy (ie, pyelonephritis, cystitis, respiratory tract infection, influenza, cough, yeast infection, venereal warts, and

genital herpes) and ASDs in a 10-year follow-up study. Although influenza infection conferred an increased risk of ASDs (hazard ratio, 2.3), this was not significant.<sup>3</sup>

Importantly, these studies differ in that the former analyzed hospital admission for infectious disease, whereas the latter analyzed only the incidence of disease. Furthermore, the former study involves physician-diagnosed disease, whereas the latter involves patient-reported illness. Nevertheless, both studies derive data from registries, thereby potentially affected by multiple confounding factors. While these are merely associations, more definitive evidence is needed to conclude with confidence that infections during pregnancy incur a risk of ASDs in offspring.

### **Bacterial Infections and Schizophrenia**

Bacterial infections have also been linked in a more robust manner with the development of schizophrenia. Sørensen and colleagues conducted a study in which the Copenhagen Perinatal Cohort was combined with the Danish National Psychiatric Register to create a cohort of 7941 neonates whose mothers were admitted for labor from September 1959 to December 1961. They conducted psychiatric follow-up and used both the strict *International Classification of Diseases, Eighth Revision (ICD-8)* definition of schizophrenia and the broader *ICD-10* categorization. Within their cohort, 87 individuals (1.1%) had a documented bacterial infection in each trimester. Among these patients, the adjusted odds ratios (ORs) of developing schizophrenia were 2.53 and 2.14 during the first trimester using the *ICD-8* and *ICD-10* criteria, respectively. The group concluded that transplacental passage of cytokines in response to bacterial infections was the seminal event that led to the development of schizophrenia as adults,<sup>4</sup> although this conclusion should be taken as merely speculative based on existing evidence. It would be interesting in future studies to test this conjecture, in order to answer multiple questions, including the following: Is the association between infection and schizophrenia trimester dependent? Which infections are involved in this pathologic presentation? And specifically, which aspects of brain development are altered to potentially cause the schizophrenic phenotype?

In summary, limited cross-sectional and cohort-based data imply a link between bacterial infections during certain critical periods of pregnancy and the development of either ASDs or schizophrenia later in life. However, because of their retrospective design, they do not demonstrate a specific causative relationship between maternal illness and fetal brain injury. This difficulty is compounded by variations in the way in which various illnesses and outcomes are defined. Finally, whether this association between infection and ASDs/schizophrenia is related only to specific types of bacterial infections and/or at certain time periods in fetal development remains unknown.

### **Viral Illnesses and the Brain**

**Influenza**—Multiple studies have, more specifically, analyzed the effects of certain types of infection and fetal/neonatal outcomes. For example, maternal influenza infection has been associated with differences in cognitive test scores and the development of both schizophrenia and bipolar disorder. For example, in a study analyzing 111 cases of individuals who ultimately developed schizophrenia or psychosis, prenatal maternal

exposure to influenza B was associated with decreased verbal IQ and scores on the Weschler Intelligence Scale information subtest at age 7 years as compared with unexposed control subjects.<sup>5</sup> In addition, Parboosing and colleagues<sup>6</sup> prospectively followed a cohort of children exposed to physician-diagnosed influenza during pregnancy and reported a nearly 4-fold increase in the risk of bipolar disorder of any subtype after exposure to influenza, irrespective of trimester, even when controlling for maternal factors, gestational age at birth, and maternal psychiatric disorders. The implication is that in utero infection can cause vulnerability in the fetal cerebral environment that may cause a susceptibility to subsequent onset of psychiatric disease. The latter of these 2 studies provides evidence that there may be an association between influenza infection and bipolar disorder; the former has limited applicability in that it reports an association between the disease and altered cognitive development only in patients who have schizophrenia or psychosis as adults. Clearly, further study is needed to confirm these findings.

### Human Immunodeficiency Virus

Maternal human immunodeficiency virus (HIV) infection has been consistently and conclusively associated with poor neurodevelopmental outcomes, specifically, cognitive and neurodevelopmental delays. A study by Msellati et al<sup>7</sup> demonstrated that in 31% of 12-month-old and 40% of 18-month-old HIV-infected children in Kigali were neurodevelopmentally delayed, as compared with 5% of uninfected control children. Most of these children had decreased gross motor function, and most had severe features of HIV-related symptoms. Another study of 65 children infected with HIV in utero showed significantly lower scores on the Mental Development Index and Psychomotor Development Index as compared with uninfected control subjects. Moreover, children with AIDS-defining illnesses other than lymphoid interstitial pneumonia performed even more poorly than did HIV-infected children either without AIDS-defining illness or with lymphoid interstitial pneumonia as their only AIDS-defining illness.<sup>8</sup> Because this latter study was performed in a population that lacked prenatal treatment for HIV, its conclusions unveil that some aspects of HIV infection itself, occurring specifically during the critical fetal periods, affect fetal brain development. These findings provide evidence that manifestations of HIV have a direct impact on the fetal brain, which affect cognitive and motor development. Further studies are needed to define how the timing and the extent of HIV infection during fetal development affect postnatal outcomes. The Pediatric AIDS Clinical Trials Group Protocol 076 showed that antepartum, intrapartum, and postnatal antiretroviral therapy with zidovudine (AZT) reduced perinatal transmission of HIV by two thirds.<sup>9</sup> Moreover, recent trials have suggested that HIV viral loads of 1000 copies/mL or greater warrant AZT treatment to significantly reduce the mother-to-infant transmission risk by 60%, whereas AZT use at lower viral loads is not recommended.<sup>10</sup>

### Hepatitis

One study of maternal hepatitis C virus infection demonstrated an increased risk of feeding difficulties (OR, 1.32; confidence interval [CI], 1.06–1.64) or some type of adverse neurological outcome in infants exposed to hepatitis C during pregnancy (OR, 1.22; CI, 1.03–1.44).<sup>11</sup> Clearly, significantly more research is necessary in understanding whether and how the hepatitis C virus affects the fetal brain.

## INFECTIONS DURING PREGNANCY AND ALTERED BRAIN STRUCTURE: EVIDENCE IN HUMANS

Another very concrete way in which human data support the link between infection and brain damage is through well-documented reports of certain anatomic abnormalities seen in the brains of individuals infected with certain bacteria and viruses. Importantly, however, these findings are not necessarily specific to in utero infection and fetal brain effects, making these associations tenuous, at best.

### Other Viral Illnesses

Some congenital viral illnesses produce distinct clinical pathology in fetal brain structure and anatomy of varying severity. For example, varicella-zoster virus infections can cause a constellation of symptoms including hydrocephalus, porencephaly, hydranencephaly, calcifications, polymicrogyria, and focal lissencephaly secondary to necrotizing encephalitis. Clinical management of uncomplicated varicella infection involves oral acyclovir or valcyclovir, whereas complications from varicella including pneumonia or encephalitis necessitate hospitalization and intravenous acyclovir.<sup>12,13</sup>

Similarly, cytomegalovirus (CMV) infections are associated with pseudocysts, microcephaly, subependymal cysts, ventriculomegaly, cerebellar hypoplasia, hypoplastic corpus callosum, lissencephaly and polymicrogyria, and periventricular calcifications that lead to necrosis and calcifications. While both maternal primary infection and reactivation of CMV in pregnancy can both cause fetal infection, approximately 10% to 20% of neonates born to mothers who have a primary CMV infection have neurodevelopmental delays and sensorineural hearing loss as children.<sup>14</sup> A randomized controlled trial by Kimberlin and colleagues<sup>15</sup> suggested that neonatal ganciclovir therapy in infants affected by congenital CMV reduced progression of hearing deterioration, but two thirds of their 100-infant cohort was found to have significant neutropenia. Given the high incidence of toxicity caused by antiviral therapy, there is no recommendation for neonatal treatment of congenital CMV. Intravenous hyperimmunoglobulin (HIG) administration to mothers affected by primary CMV infection has emerged as a novel, yet investigational, treatment to reduce neonatal clinical manifestations of infection. Three studies out of Italy suggest the safety and effectiveness of HIG therapy. The first 2 studies included only 37 and 32 subjects, respectively. Nigro and colleagues<sup>16</sup> showed a reduced risk of maternal-to-neonatal CMV transmission (OR, 0.32; CI, 0.10–0.94). The same group performed a case-control study including infants who had either hearing loss and/or psychomotor retardation and compared them with matched control subjects. The odds of developing congenital CMV infection manifestations were higher in the case group versus control subjects (OR, 14; CI, 1.7–110).<sup>17</sup> The largest and most recent study included 592 women with primary CMV infection prior to 17 weeks' gestational age. At 1 year of age, 13% of offspring from treated mothers versus 41% from nontreated mothers presented with hearing loss or neurological deficits.<sup>18</sup> All the studies may indicate a role for HIG therapy but are limited by their designs. The CHIP trial randomized 124 women with primary CMV infection to receive HIG or placebo; the rate of congenital infection was similar for both groups: 30% for the HIG group versus 44% for the placebo, with a higher rate of obstetric adverse outcomes in the HIG group.<sup>19</sup>

More trials need to be conducted to make a recommendation for all pregnant women infected with primary CMV.

Enterovirus infections are associated with hydrocephalus.<sup>20</sup> Finally, lymphocytic choriomeningitis virus can result in various abnormalities in brain structure, including microcephaly, periventricular calcifications, pachygyria, cysts, and hydrocephalus, as well structural and functional abnormalities of the eye.<sup>21</sup>

### **Bacterial and Parasitic Illnesses**

Certain bacterial and parasitic illnesses, similar to viral illnesses, are also associated with alterations in brain development. For example, syphilis is associated with hydrocephalus, whereas toxoplasmosis is associated with diffuse calcifications in the basal ganglia, periventricular calcifications, and progressive hydrocephalus.<sup>20</sup> Currently, patients are screened for syphilis in high-risk areas or if symptoms arise and can be adequately treated with penicillin. Similarly, although toxoplasmosis infections are rare, their sequelae are common among infected infants and can be similarly avoided via maternal education regarding cooking of meat and use of gloves when in contact with soil or cats.

Toxoplasmosis infections, if detected, can be treated with spiramycin, sulfadiazine, and leucovorin.<sup>22</sup>

## **ASSOCIATIONS BETWEEN CYTOKINES AND CHORIOAMNIONITIS AS MARKERS OF INFECTION AND FETAL BRAIN DEVELOPMENT**

Infections activate inflammatory pathways, causing the release of various proinflammatory biomarkers such as cytokines, interleukins, and other molecules. This inflammatory response can be measured in the setting of pregnancy through histological changes (eg, microscopic evidence of infection in the amniotic fluid or umbilical cord) or physiologic responses (eg, clinical evidence of infection including fever, fetal or maternal tachycardia, or fundal tenderness). All of these indicators of infection and inflammatory processes have also been associated with adverse neurological outcomes. Such studies give further evidence for the theory that maternal infection during pregnancy may result in inflammation/infection-mediated fetal brain damage and therefore potentially alter cognitive and psychological function later in life.

### **Cytokines**

#### **Background: Cytokines and the Function of Cytokines in Brain Development**

—Cytokines are molecules produced by cells involved in the inflammatory pathway. They act to modulate the immune response by binding to receptors and causing the release of additional cytokines in a cascade-like mechanism. They are defined by their primary cellular origin: T-helper type 1 (T<sub>H</sub>1), functioning in cell-mediated immunity against intracellular pathogens; T<sub>H</sub>2, functioning to promote humoral immunity against extracellular pathogens; T<sub>H</sub>17 or proinflammatory cytokines, involved in the mediation of septic shock; and T-regulatory cytokines, involved in dampening and shutting off the inflammatory response. Generally speaking, the T<sub>H</sub>1 axis includes interleukin 2 (IL-2), tumor necrosis factor [beta] (TNF-[beta]), and interferon [gamma]. The T<sub>H</sub>2 axis includes IL-4, IL-5, IL-6, IL-9, IL-10,



and IL-13; the T-regulatory axis includes IL-1 antagonist, transforming growth factor [beta]; and the T<sub>H</sub>17/inflammatory axis includes IL-1[beta] and IL-17.<sup>23,24</sup>

Proinflammatory cytokines can cause (1) direct damage to oligodendrocytes and neurons via the activation of microglial cells, (2) neurotoxicity, and (3) neurobehavioral abnormalities.<sup>25,26</sup> One of the most commonly studied cytokines in the context of maternal infection and brain development is the proinflammatory cytokine, IL-6. Interleukin 6 is involved in the survival of various neurons, including acetylcholinesterase-positive, catecholaminergic, cholinergic, and dopaminergic neurons. It has also been shown that IL-6 can affect the electrical mechanism by which Purkinje and enteric neuron function.<sup>27–34</sup>

**Evidence of the Relationship Between the Inflammatory Cytokine Response in Pregnancy and Fetal Brain Injury: Human Data**—Maternal cytokines dictate the type and severity of immune responses, which can portend brain pathology. In the setting of inflammation, elevations in IL-6, IL-8, and TNF-[alpha] are correlated with the development of cerebral palsy (CP) and schizophrenia and autism.<sup>35,36</sup> In addition, Gomez and colleagues<sup>37</sup> showed that neonates with a systemic fetal inflammatory response have elevated levels of IL-6 (14.0 vs 5.2 pg/mL) and suggested that IL-6 is an independent risk factor for severe neonatal morbidity. Significantly more study of the relationship between the cytokine response and the human fetal brain is needed to confirm this hypothesis.

### **Cytokines and the Fetal Brain: Evidence From Animal Models**

**Background: Animal Models:** Some of the ways in which cytokine responses have been measured in response to infection is through animal models. While we have mentioned some models in the context of specific examples above, we now give a more detailed view of these models and how they advance our understanding of the pathophysiology of inflammation and fetal brain damage. One common method of mimicking infection in animal models is through the exposure of modified proteins, which are released in the setting of infection. Specifically, lipopolysaccharide (LPS) is a component of gram-negative bacteria that mimics bacterial infections in pregnant mice. Lipopolysaccharide exposure induces the production of IL-6, TNF-[alpha], IL-1[beta], and stress hormones, including corticosterone (COR).<sup>38</sup> Similarly, polyinosinic:polycytidylic acid [poly(I:C)] is a synthetic double-stranded RNA that mimics viral infection in pregnant mice.<sup>39</sup>

**Findings From Animal Models:** There are certain lines of evidence derived from such stress models that give clues as to the potential mechanistic links between inflammation and fetal brain injury. For example, 1 animal model in which IL-6 was injected in utero on day 12.5 gestational age in pregnant mice reported behavioral, histological, and gene expression changes that led to downstream neurological sequelae. Mice injected with anti-IL-6 antibodies and IL-6 knockout mice did not show the same degree of behavioral deficiency as the wild type, thereby demonstrating the maternal immune activation caused by IL-6 injection in this model was likely the causative factor in inflammation-induced abnormal brain development. This study not only corroborates maternal immune activation as a key mechanism of fetal cerebral pathology, but it also heralded a new model by which to study the mechanism.<sup>40</sup> Further defining the mechanism of infection-related fetal brain injury is

the knowledge that prenatal IL-6 exposure during late pregnancy has 3 biochemical effects in the hippocampus: increased expression of IL-6, increased [gamma]-aminobutyric acid (GABA) receptor expression, and increased *N*-methyl-D-aspartic acid (NMDA) receptor expression. These alterations in mRNA expression ultimately result in the perpetuation of hippocampal neuronal loss and therefore altered hippocampal structure and morphology.<sup>41</sup> The expressions of GABA and NMDA are tightly regulated and are known essential components of neurogenesis and neuronal communication. Any alterations to their translation have been associated with anxiety or depression.<sup>42–45</sup> Finally, a third animal model reported that mast cell and microglial proliferation leads to the up-regulation of inflammatory cytokines such as TNF-[alpha] and IL-8, which can, in turn, cause focal brain inflammation.<sup>46</sup> This mechanism has been shown to be a precursor of ASDs.<sup>47</sup>

Thus, these types of neuroinflammatory models help to elucidate aspects of the causative mechanisms between inflammation, cytokine response, structural brain injury, and ultimately behavioral development. Ultimately, these studies may allow for confirmation that such etiologic pathways occur during human development as affected by maternal inflammatory responses. Further studies are needed to determine which causes of inflammation, for example, infectious or otherwise, are potentially linked with the type of altered brain development regulated by IL-6, NMDA, and GABA reported in animal models.

We have shown above that IL-6 has a key role in neuronal survival and mechanism to various subsets of neurons. In fact, glucocorticoids also have an essential function in normal brain development, survival, and differentiation of neuroblasts.<sup>48–50</sup> Interleukin 6 and COR can cross the placenta and the blood-brain barrier.<sup>51,52</sup> The prevailing theory lies in the elevations of IL-6 and COR, which mediate events that cause damage or an alteration in brain function, leading to neurodevelopmental damage to offspring. For example, a study of the enzyme <sup>11</sup>[beta]-hydroxysteroid dehydrogenase 2, which breaks down cortisol during times of stress and is abundantly expressed in the fetal brain and placenta, showed that it serves as a regulatory filter to limit the amount of cortisol transfer to the fetus at the fetal-maternal interface, preventing damage to mitotically active brain cells.<sup>53</sup> Perhaps this finding may spur future research to elucidate whether this enzyme is somehow down-regulated, or its function altered, by maternal infection during pregnancy.

Finally, the aforementioned brain models in which LPS and poly(I:C) are used to mimic bacterial and viral infections, respectively, have also given some evidence to support a relationship between infection and fetal brain injury. One study reported that administration of IL-1 and IL-1 receptor antagonist causes competitive inhibition of IL-1 and therefore reduced LPS-induced dysfunction in rat microglial density and motor skills, while providing better survival.<sup>54</sup> Similarly, expression of the regulatory IL-10 has been shown to ameliorate the effects of poly(I:C)-associated behavioral abnormalities in a mouse model.<sup>55</sup>

**Human Evidence of Cytokines Affecting the Fetal Brain:** In humans, several case-control studies have demonstrated an association between cytokines and neurological disease.



With respect to schizophrenia, an implication has been made that higher levels of the cytokine IL-8, measured in maternal blood during the second trimester, are predictive of the presence of schizophrenia spectrum disorders in a nested case-control study. Specifically, in a sample of 59 mothers with 105 matched comparison samples for each category of schizophrenia spectrum disorder, the average IL-8 level was found to be nearly twice that measured in mothers whose children did not develop schizophrenia. Of interest, IL-1[ $\beta$ ], tumor necrosis factor [ $\alpha$ ], and IL-6 did not show a significant association.<sup>56</sup> In addition, Ellman and colleagues<sup>57</sup> reported that individuals with a diagnosis of schizophrenia who had a prior exposure to elevated maternal serum IL-8 levels in utero had increased ventricular cerebrospinal fluid volume, decreased left entorhinal cortex volumes, and decreased right posterior cingulate volumes. Collectively, these 2 studies give support to an association between IL-8 and schizophrenia. However, a cohort study of cytokines measured at the time of delivery and patients with potential markers for psychosis showed no significant differences in IL-1, IL-2, IL-6, or IL-8 levels among the subjects studied.<sup>58</sup> Clearly, significantly more research is needed to understand the cytokine response during pregnancy and its potential downstream effects on the fetal brain, specifically because existing evidence is not specific to the association between fetal brain injury and maternal infection, and it currently does not account for the complicated and fluctuating dynamics of the cytokine response.

### Inflammation and Chorioamnionitis

**Background: Inflammation, the Fetal Inflammatory Response Syndrome, Chorioamnionitis, and the Fetal Brain**—Studies of preterm birth have coined the term *fetal inflammatory response syndrome* (FIRS), a condition characterized by systemic activation of the fetal innate immune system. It was originally defined in fetuses with preterm labor or premature rupture of membranes as an elevation in the concentration of IL-6 in fetal plasma.<sup>37</sup> Histopathologic hallmarks of FIRS include funisitis and chorionic vasculitis. Fetuses with FIRS are known to have an elevated risk of preterm labor in the setting of preterm rupture of membranes, regardless of the presence or absence of intra-amniotic infection. It has been proposed that ascending IUI results in local inflammation and the release of various proinflammatory cytokines and can also cross membranes to affect the fetus and initiate the FIRS.<sup>58</sup> The FIRS is also associated with elevations in IL-6, IL-8, and TNF- $\alpha$ . The intrauterine inflammation that is associated with infectious causes of preterm birth leads in some cases to an FIRS characterized by elevated proinflammatory cytokine levels; this pathway is associated with the development of periventricular leukomalacia (PVL).<sup>37,58–61</sup>

Chorioamnionitis is the process of active infection within the amniotic cavity that can also induce a fetal inflammatory response and affects up to 10% of pregnancies. The inflammatory process underlying maternal IUI is the quintessential mechanism of a significant portion of perinatal brain injury and a leading risk factor for neonatal sepsis.<sup>62</sup> Studies investigating the pathogenesis of the sepsis cascade have unveiled IL-1[ $\beta$ ] as the biomarker mediating brain injury in utero.<sup>63</sup> Macrophages, monocytes, and activated platelets can all release IL-1[ $\beta$ ], which works in 2 predominant pathways. Interleukin 1[ $\beta$ ] has both paracrine and endocrine effects. The former elicits the coagulation cascade,

recruitment of other interleukins, and activation of T cells. The latter can decrease blood pressure and induce fever by releasing prostaglandins. Not only have animal models recapitulating IUI shown an increased expression of IL-1[ $\beta$ ] expression in the fetal brain and placenta, but also IL-1[ $\beta$ ] receptor blockade prevents fetal cortical brain injury.<sup>64</sup>

Despite its perinatal predisposition, chorioamnionitis is thought to result in not only short-term but also long-term neurodevelopmental disabilities. Such long-term outcomes include increased neonatal death rate, respiratory distress syndrome, PVL, and CP. The unifying hypothesis is the overwhelming fetal production of cytokines that leads to, among other organs, brain cell damage.<sup>65</sup>

Clinical evidence of chorioamnionitis has been significantly associated with both CP and cystic PVL (cPVL), and histological chorioamnionitis has been similarly associated significantly with cPVL.<sup>65</sup> Models of preterm birth by Burd and colleagues<sup>66</sup> had demonstrated that inflammation-induced preterm birth by LPS, in which preterm birth is induced by intrauterine inflammation, is associated with fetal neuroinflammation, whereas noninfectious induction of preterm birth by RU486 (an antiprogesterone agent) is not associated with such outcomes.

**Chorioamnionitis, Inflammation, and the Brain: Human Data**—There exists a large body of evidence in humans that clinical and histological chorioamnionitis may contribute or predispose to fetal brain injury and disease. One meta-analysis evaluated the role of chorioamnionitis with respect to cPVL, a precursor to CP in preterm infants. The data suggested that clinical chorioamnionitis conferred a significant risk of CP (relative risk [RR], 1.9) and cPVL (RR, 3.0), whereas histological chorioamnionitis only was significant for cPVL (RR, 2.1).<sup>67</sup> A review of studies of placental pathology noted that several studies have reported a relationship between intraventricular hemorrhage and histological ascending IUI (maternal and fetal response). A meta-analysis of studies of white matter injury in preterm infants reported an RR of 2.1 for development of these outcomes in cases of clinical and histological ascending IUI. Thrombotic vasculopathy and funisitis are associated with neonatal encephalopathy. In addition, in infants of extremely low gestational age, histological inflammation is predictive of ventriculomegaly and diplegic CP. Term infants with evidence of ascending IUI with funisitis have also been reported to have an increased risk of neurological impairment (OR, 2.9–13.2; CI, 1.2–144), and preterm children at toddler age have been reported to have higher incidence of moderate to severe disability including speech abnormalities and hearing loss.<sup>68</sup> The clinical management of acute chorioamnionitis infection should prompt the institution of intravenous antibiotics and delivery of fetus. However, the details of delivery and exact timing are not defined. Gibbs and colleagues<sup>69</sup> implemented a policy of cesarean delivery only for routine obstetric indications and saw a mean time of delivery between 3 and 5 hours, with 90% of patients delivered within 12 hours of diagnosis. Although no critical interval was identified, lower morbidity was seen in neonates born vaginally. As to timing of antibiotic administration, 3 studies show an advantage of intrapartum administration of ampicillin and gentamicin with clindamycin added for cesarean delivery at cord clamping.<sup>70–72</sup> There is some evidence indicating a positive effect of a complete antenatal corticosteroid course in ameliorating the postulated effects of in utero inflammation on the fetal brain. Specifically, 1 study of 225

infants of less than 30 weeks' gestational age noted that CP was associated with in utero inflammation in infants not treated with steroids, but not in those treated with steroids.<sup>73</sup> In addition, scant evidence exists suggesting that N-acetylcysteine may provide neuroprotection in the setting of chorioamnionitis.<sup>74</sup>

Further study is needed in this area to define which causes of chorioamnionitis ultimately lead to such outcomes. More long-term follow-up data will be required to determine whether some of the adult psychiatric disease described as associated with maternal infection at the beginning of this article can be linked with the pathophysiology of chorioamnionitis.

## CLINICAL IMPLICATIONS

Currently, there is very little that is empirically proven to prevent the postulated effects of neonatal infection and inflammation on brain injury. While vaccines and patient education are important tools for prevention, the various treatment recommendations for neonatal intrauterine neuroinflammation come up short of improving short- and long-term outcomes, let alone eradicating the inciting pathogen.<sup>22</sup>

## SUMMARY AND CONCLUSIONS

In conclusion, various types of evidence support the theory that maternal infection and/or inflammation occurring during critical periods of fetal development could alter brain structure and function in a time-sensitive manner. Specifically, in humans, bacterial infections during pregnancy have been weakly associated with abnormal psychological and cognitive development in their offspring, and both bacterial and viral infections are associated with abnormal brain structure in affected individuals. Both retrospective human data and findings from animal models suggest potential causative mechanisms for the association between infection and fetal brain injury; specifically, infection induces an inflammatory cascade characterized by elevations in critical cytokines such as IL-6, ultimately resulting in altered brain structure and function. Moreover, findings linking the histological and clinical markers of fetal and maternal infection in the setting of chorioamnionitis with alterations in psychiatric and neurological development further support this theory. Figure 1 shows a schematic summarizing the various causes of fetal brain injury.

Ultimately, these pieces of evidence all support the hypothesis that maternal infection during pregnancy can have direct effects on the fetal brain, ultimately resulting in psychologic and cognitive disease. Future studies are necessary to more clearly and specifically define the causative mechanisms between inflammation, infection, brain development, and cognitive/psychologic function in humans. For example, the causative mechanisms of cytokine elevation and brain injury seen in animal models need to be translated to studies of those cytokines in human fetuses specifically in the context of particular infections of interest. Such information will be critical in the future for targeting treatment strategies to promote normal healthy brain development in fetuses exposed to infections in utero.

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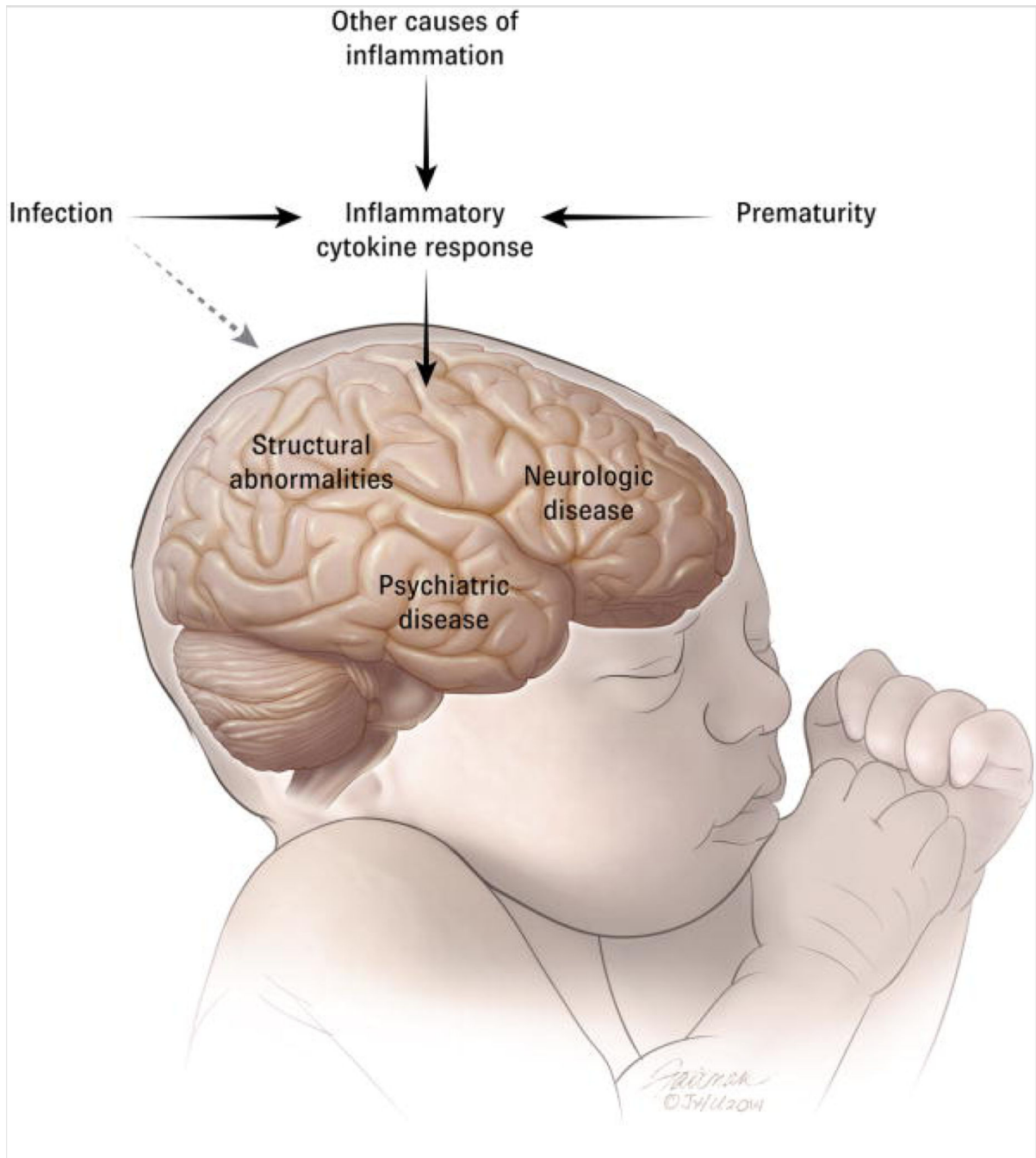
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### Learning Objectives

After completing this activity, the learner will be better able to demonstrate that human brain development occurs throughout the fetal period and can be altered by infection and inflammation in ways that are dependent on the nature and timing of the insults; discuss the various maternal infections that are associated with adverse neurological outcomes, including schizophrenia and autism; discuss the viral, parasitic, and bacterial infections that are associated with altered brain structure and anatomy in both human and animal models; and demonstrate that chorioamnionitis is associated with altered brain and neurological development.



**FIG. 1.** Fetal brain is affected by infections and inflammation during critical times of development (prematurity), which may lead to structural abnormalities as well psychiatric and neurological diseases.

TABLE 1

Schematic of Various Causes of the Inflammatory Cytokine Response Affecting Anatomical and Functional Neonatal Outcomes

Infection	Fetal Findings	Long Term Effects	Citation
Viral			
CMV	Periventricular calcifications, pseudocysts, and necrosis, microcephaly, subependymal cysts, ventriculomegaly, cerebellar hypoplasia, hypoplastic corpus callosum, lissencephaly, polymicrogyria		5,15
Herpes simplex virus	Extensive cerebral cortical calcifications, possible microcephaly, encephalomalacia, hydrocephaly	Mental retardation, severe neurological deficits, encephalitis	6
HIV		Neurodevelopmental delay, especially gross motor function  Poor performance on cognitive tests, decreased processing speed and visual spatial task performance  Lower scores on Mental Developmental Index and Psychomotor Development Index	12,13
Influenza		Decreased IQ and Weschler Intelligence Scale information test scores at age 7 y  Bipolar disorder (statistically significant in third trimester infections)  Infantile autism	3,10,11
Lymphocytic choriomeningitis virus	Microcephaly, periventricular calcifications, pachygyria, cysts, and hydrocephalus, as well structural and functional abnormalities of the eye	Seizures Neurodevelopmental delay Nystagmus Strabismus esotropia or exotropia	21
Hepatitis C		Feeding difficulties or other adverse neurological outcomes	14
Enterovirus	Hydrocephalus		15
Varicella zoster	Hydrocephalus, porencephaly, hydranencephaly, calcifications, polymicrogyria, and focal lissencephaly secondary to necrotizing encephalitis		15
Bacterial			
Syphilis	Hydrocephalus		15
Rubella	Extensive cerebral cortical calcifications, microcephaly, subependymal cysts		15
Parasitic			
Toxoplasmosis	Diffuse calcifications in the basal ganglia, periventricular calcifications, progressive hydrocephalus		15
Illness, generally defined	Increased length of cavum septum, pelucidum after midgestation influenza, toxoplasma antibody titers, second-trimester respiratory illness, or periconceptual genital infection  Ventricular enlargement secondary to brain substance loss/hypoplasia and/or cerebrospinal fluid drainage defects	Psychotic symptoms at age 12	7,8,15
Maternal anti-inflammatory use		Schizophrenia	7
Maternal febrile episode		Autism (If fever > 1 wk <32-wk gestation)	3

Infection	Fetal Findings	Long Term Effects	Citation
Maternal antibiotic use		Autism (second- or third trimester sulfonamide use)	3
Chorioamnionitis	Intraventricular hemorrhage, white matter injury associated with IUI	Neonatal encephalopathy associated with funisitis	60
	CP in 28% of preterm and 12% of term infants	Diplegic CP in infants of extremely low gestational age with histological inflammation	
	Ventriculomegaly in infants of extremely low gestational age with histological inflammation	Increased risk of neurological impairment in term infants with funisitis	
		Moderate to severe disability, including speech abnormalities and hearing impairment, in toddler-age preterm children with funisitis	