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Title

The Fetal Origins of Mental Illness

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This review summarizes new evidence for how infections during pregnancy can alter fetal brain development and predispose the child to mental illness decades after birth.

Short Version of the Title

Fetal Origins of Mental Illness

Abstract:

The impact of infections and inflammation during pregnancy on the developing fetal brain remains incompletely defined with important clinical and research gaps. Though the classic infectious TORCH pathogens [i.e. *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), herpes simplex virus] are known to be directly teratogenic, emerging evidence suggests that these infections represent the most extreme end of a much larger spectrum of injury. We present the accumulating evidence that prenatal exposure to a wide variety of viral and bacterial infections – or simply inflammation – may subtly alter fetal brain development, leading to neuropsychiatric consequences for the child later in life. The link between influenza infections in pregnant women and an increased risk for development of schizophrenia in their children was first described more than 30 years ago. Since then, evidence suggests that a range of infections during pregnancy may also increase risk for autism spectrum disorder and depression in the child. Subsequent studies in animal models demonstrated that both pregnancy infections and inflammation can result in direct injury to neurons and neural progenitor cells or indirect injury through activation of microglia and astrocytes, which can trigger cytokine production and oxidative stress. Infectious exposures can also alter placental serotonin production, which can perturb neurotransmitter signaling in the developing brain. Clinically, detection of these subtle injuries to the fetal brain is difficult. As the neuropsychiatric impact of perinatal infections or inflammation may not be known for decades after birth, our construct for defining teratogenic infections in pregnancy (e.g. TORCH) based on congenital anomalies is insufficient to capture the full adverse impact on the child. We discuss the clinical implications of this body of evidence and how we might place greater emphasis on prevention of prenatal infections. For example, increasing uptake of the seasonal influenza vaccine is a key strategy to reduce perinatal infections and the risk for fetal brain injury. An important research gap exists in understanding how antibiotic therapy during pregnancy impacts the fetal inflammatory load and how to avoid inflammation-mediated injury to the fetal brain. In summary, we discuss the current evidence and mechanisms linking infections and inflammation with the increased lifelong risk of neuropsychiatric disorders in the child, and how we might improve prenatal care to protect the fetal brain.

Keywords: pregnancy, infection, inflammation, fetus, brain, schizophrenia, depression, autism, influenza virus, urinary tract infection, TORCH, microglia, neuronal injury, seasonality of birth hypothesis

Introduction

The impact of infection and inflammation on the developing fetal brain is poorly understood but is thought to increase the lifetime risk for some types of mental illness. The severe infectious teratogens known by the acronym TORCH [e.g. *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus] have commanded a focal point in obstetrics due to their potential to cause catastrophic structural anomalies in the fetal brain including anencephaly, ventriculomegaly, deafness, and ocular injury.[1–5] However, evidence that other perinatal infections may increase the lifetime risk of schizophrenia for the fetus has accumulated for more than half a century.[6] By the 1960s, several studies found a slight increase in the incidence of schizophrenia among children and adults that had been born during the winter months in both northern and southern hemispheres, suggesting a link with viral infections more prevalent during the winter.[6–8] These observations led to a "seasonality of birth" hypothesis suggesting that some proportion of adult schizophrenia was caused by virus-induced fetal brain injury.[9]

Subsequent studies in humans and mouse models linked prenatal exposure to single pathogens, complex infections, and inflammatory disorders with changes in fetal brain development leading to a wide spectrum of cognitive deficits and neuropsychiatric disorders including autism spectrum disorder (ASD).[10,11] Recently, the concerning finding that maternal hospitalization with *any* infection in pregnancy, including urinary tract infections, increased risk of ASD and depression in the exposed offspring suggests that the fetal brain may be more vulnerable than previously thought to a wide variety of infections.[11] Overall, it appears that a broad category of infectious and inflammatory events in pregnancy can result in an increased risk of neuropsychiatric disease for exposed children. This evidence requires a reconception of infectious risks during pregnancy beyond those imparted by TORCH pathogens. In this review, we aim to highlight what is currently known about the fetal infectious and inflammatory origins of mental illness. We also discuss the clinical and research implications of how we might reconsider infection prevention and treatment with an emphasis on protecting the fetal brain.

Infectious Prenatal Origins of Schizophrenia, Autism Spectrum Disorder, Bipolar Disorder and Depression

Schizophrenia

The earliest studies of psychiatric disease after exposure to infection *in utero* focused on schizophrenia. This disorder is typically first diagnosed in early adult life and has been associated with events occurring early in brain development; accordingly, many studies have focused on pregnancy complications and the role of infectious exposures.[12] Evidence for the fetal origins of schizophrenia risk include: numerous studies of *in utero* infection across trimesters,[13] an archival cohort study of gestational starvation during the so-called "Dutch Hunger Winter" of Nazi occupation,[14] data from the famine years in China's Anhui Province,[15] and studies on the effect of smoking[16] and limited maternal weight gain.[17] In the 1960s and 1970s, multiple studies found an increased incidence of schizophrenia among adults born during the winter months, suggesting an association with fetal exposure to maternal viral infections; these and other studies culminated in a "seasonality of birth" hypothesis for the etiology of schizophrenia.[6–9,18–21]

The 1957 influenza pandemic offered an opportunity to study the long-term mental health outcomes of adults who were likely to have been prenatally exposed to influenza. In a study of Finnish adults, there was a markedly higher risk of hospitalization for schizophrenia in adults who were fetuses in the second trimester during the peak of the 1957 influenza epidemic compared to adults who were born in the 6 years prior to the epidemic.[22] This "second trimester" effect was observed independently across several greater Helsinki psychiatric hospitals and occurred in both men and women. Subsequent studies focused on serologic testing as a method to link schizophrenia with perinatal exposure to a variety of microbes.[23–27] Overall, these studies strongly implicated perinatal infections and complications as risk factors for schizophrenia, but were limited by insufficient power and were mainly exploratory in nature. Significant variability in study exposures and subjects has made systematic reviews of this body of

work difficult to interpret, but the preponderance of evidence suggests that prenatal infection and inflammation play important roles in some proportion of schizophrenia.[28]

Autism

Several systematic and meta-analytic reviews provide converging evidence that infections during pregnancy elevate the risk for ASD in the offspring.[29–31] A meta-analysis of 15 studies with more than 40,000 ASD cases demonstrated an increased risk for ASD after prenatal exposure to infection (OR = 1.13, 95% confidence interval (CI): 1.03–1.23)), particularly when the mother was hospitalized for the infection (OR = 1.30, 95% CI: 1.14–1.50).[31] The largest of these studies in the meta-analysis could not determine whether the timing of infection during pregnancy was important, but was likely underpowered to detect trimester effects.[34] Prenatal fever has also been associated with development of ASD in the Norwegian Mother and Child Cohort Study (114,500 pregnant women). In this study, a second trimester prenatal fever was associated with a 1.40 adjusted odds ratio [aOR; 95% confidence interval (CI) 1.1-1.8]; multiple fevers were associated with an even higher risk of ASD (aoR 3.1, 95% CI 1.3-7.6 with 3 or more fevers). Animal models of both viral and bacterial infections in rodents and rhesus macaques support these findings; maternal infections have been associated with ASD-like phenotypes in the offspring with reduced socialization, atypical vocalizations, and repetitive behaviors.[35–45] Both maternal and immune system dysfunction have emerged as central mechanisms that tie together many of the proposed environmental and pregnancy risk factors for ASD.[32] For example, there is a clear linkage between the inflammatory response and both environmental toxicants[46–48] and obesity.[49,50] Meta-analyses also consistently demonstrate small, but significant and precise associations of family history of autoimmune disorders and ASD in offspring.[51,52] Further, sexually dimorphic differences in the differential expression of innate immune genes in the brain are implicated in the strong male bias for ASD.[53–55] Overall, the evidence supports a role for prenatal infections and other sources of maternal-fetal immune activation in the fetal origins of ASD.

Bipolar Disorder and Depression

The link between exposure to prenatal infections and development of bipolar disorder and depression is less clear. While there have been several studies to determine whether maternal infections during pregnancy increased the risk of bipolar disorder in the child, the results have been mixed and suffered from insufficient power and lack of correction for multiple hypothesis testing.[56–58] In at least one study, maternal influenza infection was not linked with development of classical bipolar disorder in the child, but instead was associated with bipolar disorder with psychotic features.[59] A recent study similarly found no increased risk for bipolar after maternal infection.[11] Reflecting this uncertainty, a systematic review of risk of bipolar disorder after perinatal infection determined that results were mixed and more research was needed.[60]

There have been comparatively few studies examining the possible increased risk for depression after prenatal exposure to inflammation or infection and the results have also been mixed.[11,58,61–70] However, many of these studies have relied on maternal self-report of infection during pregnancy or have studied depression outcomes of adults born during epidemics. Recent evidence from a population-based cohort in Sweden demonstrated increased risk of depression after fetal exposure to any type of hospitalized maternal infection (Hazard Ratio=1.24; 95%CI: 0.88-1.73) including urinary tract infections.[11] Separate observational data from the Swedish death registry demonstrated an increased risk of suicide starting at age 21 years among adults who had been exposed to a maternal infection during a hospitalization *in utero*.[11] In addition, multiple studies in mouse models have found that fetal mice exposed to maternal immune activation may demonstrate depression-like behaviors.[71–77] Overall, the evidence that prenatal infections underlie the fetal origins of depression is emerging and warrants more investigation.

Mechanisms of Fetal Brain injury

Many bacteria, viruses and parasites can cause direct or indirect injury to the fetal brain resulting in mild and severe neurodevelopmental injuries (Figure 1). The classical

TORCH infections are known to cause direct injury to fetal brain cells by crossing the placenta and concentrating within the fetal compartment. These pathogens can cause varying degrees of injury to the cortical white matter, eye, and ear[78], resulting in a broad spectrum of pathology, from mild hearing deficit to severe neurodevelopmental delay.[79] However, many infectious diseases can also injure the fetal central nervous system indirectly by potentiating the fetal inflammatory response resulting in activation of astrocytes and microglia causing cytokine release, apoptosis, attenuation of growth, and direct cellular damage (see CMV example, Figure 2).[78] Placental inflammation is a key feature associated with fetal brain injury; inflammatory mediators or cells in the placenta can be transferred to the fetus, which can ultimately injure the fetal brain either through release of fetal cytokines, neurotransmitters or excitotoxic metabolites (Figures 2 and 3). To understand the pathogenesis of subtle fetal brain injuries that contribute to the future risk of mental illness, we review the linkage between perinatal infections, placental inflammation, activation of astrocytes and microglia in the fetal brain, genetic predisposition and epigenetic modifications.

Placental inflammation

Among the mechanisms implicated in fetal brain injury, evidence strongly indicates that the immunologic milieu of the placenta plays an important role in neurodevelopment. Placental mediation of immune activation was suggested by a study finding a higher concordance of schizophrenia among monochorionic twins sharing one placenta compared to dichorionic twins, each with its own placenta.[80] A recent study demonstrated that many perinatal complications including infections can upregulate transcriptional programs in the placenta involved in oxidative stress response, synaptic function and cellular metabolism.[81] Suggestively, these same genetic loci are critical for normal neurodevelopment, and are also independently upregulated in patients with schizophrenia. The genetic risk for schizophrenia appears to be mediated through these perinatal complications such that a diagnosis of schizophrenia was most likely when a patient with a high genetic risk also experienced a perinatal complication; this effect was more pronounced in males. Taken together, these findings suggest that pregnancy

complications and presumably inflammation may alter placental regulation of transcriptional programs, which can increase risk for development of schizophrenia.[81]

Both adaptive and innate immune responses in the placenta have been linked with the fetal origins of mental illness. $CD8^+$ T cell infiltration of the placenta has emerged as a key immunological event following viral infection that can have destructive effects on the placental villous architecture and the chorioamniotic membranes.[82] Following lipopolysaccharide-induced intrauterine inflammation in a mouse model, $CD8^+$ T cells accumulated at the maternal-fetal interface; treatment with an anti-inflammatory led to reduced $CD8^+$ T cell infiltration and improved fetal neurobehavioral outcomes.[83] Depletion of CD8+ T cells in the same model of intrauterine inflammation was also associated with improved fetal neurologic outcomes and increased cortical neuron density.[84] Less is known about the contribution of innate immune responses to the fetal origins of mental illness and the specific role of inflammatory cytokines,[32,85,86] but there is some evidence that TGF-β1 and granulocyte colony-stimulating factor may cross the placenta to enter the fetal circulation.[87–90] Emerging evidence suggests that IL-17A and IL-2 also play important roles in fetal brain injury.[35,91–93] The best support for a role for cytokines in the biology of neuropsychiatric conditions comes from studies of children and adults diagnosed with ASD, in whom interleukin-6 (IL-6) is elevated in the peripheral blood.[94–101] IL-6 can cross the placenta[94,95] and administration of IL-6 can cause behavioral abnormalities in prenatally exposed mice in the absence of maternal inflammation, which is preventable by IL-6 inhibition.[101,102] Activation of both innate and adaptive immune responses in the placenta and periphery are associated with adverse neuropsychiatric outcomes.

Serotonergic dysregulation

The placenta is known to secrete neurotransmitters, which are linked with normal fetal brain development and abnormal neurodevelopment. In mice, maternal inflammation changes placental serotonin secretion which results in concentration of serotonin in the

fetal forebrain, decreased serotonergic receptor expression and blunted serotonergic axon outgrowth.[103] Fascinatingly, this process appears to occur in the absence of increased levels of inflammatory cytokines within the fetal brain.[103–105] Other work has demonstrated a connection between elevated levels of serotonin and altered oligodendrocyte development and myelination.[106] Maternal inflammation has also been found in animal studies to change dopaminergic and GABAergic activity in the fetal brain, which correlates with observations from human studies in people with schizophrenia and ASD.[107–112] Lastly, maternal immune activation may also change development of cholinergic neurons in the fetal basal forebrain.[113] The connection between maternal infections or inflammation, placental neurotransmitter secretion, and fetal brain development is an active area of investigation.

Activated microglia, astrocytes and oligodendrocytes

Perinatal inflammation can activate fetal microglia and astrocytes to trigger cytokine release, which can injure neurons and oligodendrocytes.[114] Histopathological studies of the brains of individuals with ASD have found microglial activation and an abnormal morphology and distribution of microglia.[99,115–118] Further, in vivo imaging has demonstrated increased microglial activity in patients with ASD[119] and other work has demonstrated possible abnormal microglia-neuron interactions.[118] In numerous animal studies, maternal inflammation induces microglial activation[113,120–122]in the fetal brain, although these findings have not been universally replicated.[123–125] In vitro studies have demonstrated increased neurotoxic cytokine release from activated microglia, which may damage or kill neurons and glia.[113] There have been findings of microglial activation in schizophrenia[126–132], though again with substantial inconsistencies, and some work has examined the role of microglia in bipolar disorder and depression.[133–135]

Astrocyte-associated pathologies are associated with exposure to pregnancy infections and development of ASD through effects on mitochondrial dysfunction, glutamate regulation and neuronal architecture.[99,114,136–139] For example, increased expression of mitochondrial potassium channels within astrocytes has been found in people with ASD;

in the fetal mouse brain, expression of these channels is also upregulated by a perinatal influenza infection.[140–142] Astrocyte dysfunction is also under investigation in depression[143,144] and schizophrenia.[144] Some organisms like *Toxoplasma gondii* may increase the risk for schizophrenia through astrocyte activation and dysregulation of kynurenic acid metabolism.[145–147] Aberrant astrocyte activation is associated with the development of neuropsychiatric disorders and fetal exposure to obstetrical infections.

Inflammatory cytokines from activated microglia and astrocytes may alter the development of fetal oligodendrocytes[148] which has been implicated in the pathology of schizophrenia, depression, ASD and bipolar disorder.[149–156] Oligodendrocytes are the myelinating cells of the central nervous system. Evidence suggests that oligodendrocyte precursor dysfunction and hypomyelination may play important roles in ASD pathophysiology.[157,158] Several recent and interesting studies are also implicating deficits in myelination and white matter integrity in the pathogenesis of schizophrenia and brain "disconnectivity".[159] Damaged oligodendrocytes and precursors from antenatal exposure to maternal immune activation may also be more susceptible to hypoxic insults over the life course and this combination may increase risk of multiple psychiatric illnesses.[160] Interestingly, genes and transcription factors associated with oligodendrocyte myelination function have been found to be downregulated in the brains of adults with schizophrenia and bipolar disorder.[161,162] In summary, there is a body of evidence to link obstetrical infections or inflammation with activation of innate immune cells in the fetal brain, which contribute to abnormal oligodendrocyte development and may increase risk for development of a spectrum of neuropsychiatric disorders in the child.

Inflammation, genetic susceptibility and epigenetics

The link between perinatal infection and fetal brain injury reflects a complex spectrum of exposure severity (e.g. pathogen virulence, maternal-fetal immune response) and genetic susceptibility that can alter brain development and predispose to ASD and schizophrenia (Figure 1).[163] Maternal immune activation can also alter fetal brain transcription through

epigenetic changes even in the apparent absence of fetal inflammation.[164] In a mouse model, inflammation that is insufficient to trigger preterm birth was associated with decreased dendritic counts and altered protein expression in the fetal brain[165], along with epigenetic changes in the mouse adolescent brain.[166] Indirect evidence from one study involving nearly 3,000 children with ASD found that interactions between maternal infection and the presence of a genetic predisposition in the child led to increased ASD symptom severity.[167] Schizophrenia has also been associated with epigenetic modifications[168–171]; epigenetics is the heritable change in gene expression that is not defined by the underlying DNA sequence, which is often accomplished through DNA methylation or histone modifications.[172] Perinatal inflammation has been associated with genome-wide methylation changes in the fetal brain[173,174] and epigenetic changes in the striatum and hypothalamus thought to increase risk for schizophrenia.[166] Inflammation-gene interactions have been found to induce psychosis-like behavior in mice[175,176]; the interaction between maternal inflammation and gene variants associated with neuropsychiatric disorders (e.g., *DISC1*, *Nurr1*) are also linked with a greater risk for psychosis-like behavior in mice than either inflammation or genetic mutation alone.[92] In a recent study of five independent cohorts of humans with diverse ancestries, perinatal complications were observed to increase the risk of schizophrenia 5-fold among fetuses with an increased genetic risk.[81] In this study, a polygenic risk profile score was constructed based on genome-wide association data from the Psychiatric Genetic Consortium datasets; this polygenic risk score was then overlaid upon the occurrence of obstetrical complications through medical records and personal interviews. When the polygenic risk scores were grouped into quintiles based on levels and then stratified into groups with and without obstetrical complications, the odds ratio for schizophrenia increased with higher polygenic risk scores only in the group with obstetrical complications. An individual having the highest polygenic risk score with an obstetrical complication had an OR of 8.4 (95% CI: 3.8-18.5, $p=3 \times 10^{-8}$). Interestingly, the genes mapping to the loci with the strongest link to schizophrenia also had significantly higher gene expression in the placenta. In summary, evidence from human studies and animal models implicate an interaction between inflammation, perinatal complications and

epigenetic changes in the fetal brain that can increase the risk for schizophrenia and ASD.

Clinical Recommendations

As data accumulate on the connection between perinatal inflammation and neuropsychiatric disease, preventing infections during pregnancy assumes greater importance (Box 1). While some perinatal infections are unexpected (e.g. chorioamnionitis), many can be prevented through vaccination including influenza, measles and chicken pox. Influenza vaccination of pregnant women is a best practice for promoting health of the mother and protecting the fetal brain. Influenza infection during pregnancy is associated with serious immediate risks (i.e. maternal mortality, preterm birth),[177,178] as well as possible long-term risks of neuropsychiatric disease in the child. Maternal vaccination also partially protects the infant through passive immunity.[179–183] The World Health Organization not only recommends that pregnant women receive the influenza vaccine, but that they have highest priority among vulnerable groups.[184]

Despite the well-established efficacy of the vaccine for maternal and neonatal protection from influenza infection, global vaccination rates among pregnant women remain low. In the United States, approximately half of pregnant women are estimated to receive the seasonal influenza vaccine.[185,186] Limited data exists outside of the United States[187], but recent European data suggested that approximately 25% of pregnant women were vaccinated.[188] Lastly, despite evidence that inactivated influenza vaccine is safe to administer in the first trimester, some countries have national policies recommending vaccination only in the second and third trimesters.[189–196] These policies leave pregnant women vulnerable to influenza infection in the first trimester, which is a critical period of fetal neurodevelopment.

Although many pathogens have yet to be studied for the risk that they could impart to the developing fetal brain, any severe maternal infection may increase the risk for neuropsychiatric disease in the fetus that may not manifest for many years after birth. Rubeola virus (measles), Zika virus, and malaria represent both new and ancient potential infectious threats to the developing fetal brain. Currently, the United States is in the midst of one of the most significant outbreaks of the measles virus since virtual eradication of measles in the U.S. in 2000.[197] Measles infection during pregnancy is linked to preterm labor, preterm birth, and stillbirth.[198–201] While pregnant women cannot receive the MMR vaccine, obstetrical providers can encourage their patients to fully vaccinate their children to promote beneficial herd immunity. Pregnant women in Zika and malaria-endemic zones should protect themselves from mosquitos using bed nets, protective clothing and mosquito repellant.[202–204] The World Health Organization recommends intermittent preventative therapy with sulfadoxine-pyrimethamine for pregnant women living in regions with middle and high malaria transmission.[205] An important part of prenatal care is discussing the fetal risks due to infections that may be acquired during travel that can result in teratogenesis or a severe maternal illness..

Further Research Directions

The studies exploring a fetal origin for mental illness have raised many questions (Box 2). Recent work has suggested that urinary tract infections (UTI) in hospitalized women may increase the risk for autism or depression to a similar degree as infections typically considered more severe (e.g. influenza infection, chorioamnionitis).[11] UTIs are the most common infection in reproductive aged women, occur more frequently during pregnancy and can be associated with serious maternal and fetal morbidity and mortality.[206,207] Interestingly, there is some evidence linking UTIs with a systemic inflammatory response and preeclampsia.[208] Other work has demonstrated that infants born to mothers with a UTI during pregnancy had elevated levels of several pro-inflammatory cytokines.[209] Maternal UTIs have also been linked to development of cerebral palsy.[210] These studies are suggestive and future work should attempt to correlate UTI-associated local and systemic inflammatory responses with inflammation in the

placenta, amniotic fluid and fetus. Animal models have typically studied the link between a systemic or uterine infection with fetal brain injury; new studies could determine whether chronic inflammation resulting from a UTI is sufficient to induce fetal brain injury and activate microglia.

Questions have also emerged on the pro and anti-inflammatory roles of antibiotics in treating bacterial infections in pregnant women. The duration and extent of the infection coupled with the choice of antimicrobial therapy may play a role in the maternal immune response and possible subsequent neurodevelopmental abnormalities in offspring. Indeed, maternal immune activation may be induced by certain antibiotics, enhancing an inflammatory response detrimental to neurological development via lipopolysaccharide and other pathogen-associated molecular patterns (PAMPs).[211] PAMPs have been studied in limited settings but early evidence suggests a possible link to worsened fetal outcomes. In a mouse pregnancy model, treatment of maternal *Streptococcus pneumoniae* bloodstream infection with ampicillin, known to be bacteriolytic and to induce release of bacterial cell wall components, resulted in abnormal fetal neuronal development.[211] Yet, treating the same maternal infection with clindamycin, a non-bacteriolytic protein synthesis inhibitor, had no effect on the fetal brain.[211] There are few experimental and epidemiological studies exploring the effect of antimicrobial treatment of systemic or local maternal infections (e.g. UTI) on brain development, but some evidence suggests that dampening pathogen-induced inflammation during pregnancy may mitigate neurodevelopmental abnormalities in offspring.[212–215] The alternative, namely not treating a bacterial infection with antibiotics, is simply not an option as this could lead to bacterial dissemination and sepsis with even worse outcomes for the mother and fetus. Overall, investigation of the role of anti-inflammatory drugs with and without antibiotic therapy coupled with fetal outcome remains a significant research gap.

Large birth cohorts with long-term follow-up of the children are essential to investigating the relationship between perinatal infections and risk for neuropsychiatric disorders in

the children. With better powered studies, it may be possible to clarify how the gestational timing of the inflammatory insult alters fetal neurodevelopment and whether this risk is modified by fetal sex.[81,216–218] Further, it is possible that some portion of more subtle pathologies like Attention Deficit Hyperactivity Disorder may have a fetal origin associated with exposure to inflammation.[219,220] Future studies are important to define the role of placental secretion of neurotransmitters and cytokines in mediating fetal injury.[102,163] Lastly, a nascent body of work is exploring how the maternal gut microbiome may interact with maternal inflammation to alter the intrauterine environment.[221,222]

Conclusions

The classic TORCH paradigm was coined to create a mnemonic to aid in the recall of a select number of pathogens (i.e. *Treponema pallidum*, rubella virus, cytomegalovirus) thought to induce birth defects. However, a growing body of evidence suggests that focusing only on TORCH pathogens as a threat to the fetal brain is insufficient to capture the widening spectrum of pathogens and inflammatory conditions associated with neurocognitive deficits or psychiatric disorders in the child. As fetal brain development continues up to and beyond birth, the brain may be the single most vulnerable fetal organ to infectious and environmental insults over the course of the entire pregnancy.[223] The nature of how fetal exposure to infections or maternal immune activation might synergistically increase the risk of these disorders with other risk factors (e.g. genetic) remains understudied. Finally, the clinical emphasis on preventing infections and inflammation in pregnancy to protect the fetal brain has not matched the gravity of the accumulating scientific evidence. Obstetrical providers should ensure that pregnant women receive the influenza vaccine, including in the first trimester, as a safe strategy to protect both the mother from severe disease, as well as the fetal brain. Determining additional interventions to lower the risk of neuropsychiatric disorders in the fetus will require both human cohorts and animal studies to correlate the complex biological events linking perinatal infections with fetal brain injury.

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1124 **Figure Legends**

Figure 1. Factors linking perinatal infections with mild and severe fetal brain injury. Several factors are thought to influence the severity and extent of a maternal infection leading to mild or severe fetal brain injury. Mild fetal brain injuries may not be detected clinically at birth and may only manifest later in life as a neurodevelopmental or neuropsychiatric disorder.

Figure 2. Photomicrographs of the placenta and fetal or neonatal brain infected with CMV. In the placenta (A), there is hyperplasia of fetal macrophages (Hofbauer cells) and infiltration with lymphocytes and plasma cells. Inclusions are shown, which are pathognomonic for CMV infection. (B) In the brainstem of a 4 month-old infant born at 26 weeks gestation with a prenatal CMV infection, a microglial nodule (within the white circle) is shown with most cells reflecting lymphocytes, activated microglia and reactive astrocytes. (C) In the white matter of a 25-day old neonate born at 24 weeks gestation with a CMV prenatal infection, a focus of remote necrosis and dystrophic mineralization (refractile dark purple deposits) is shown. (D) In the fetal brain of a 23-week fetus, the acute phase of a CMV infection is shown with a hypercellular focus containing a mixture of activated microglial cells, reactive astrocytes, and a presumed neuron with pathognomonic CMV cytoplasmic and nuclear inclusions. A measurement bar representing 100 um is shown in panel C, which is applicable to all panels.

Figure 3. Perinatal infections, placental immune response and cellular targets in the fetal brain. A spectrum of maternal infections induced by viruses, bacteria and parasites have been implicated in the development of placental pathology and fetal brain injury. Infiltration of the placenta by immune cells, notably maternal CD8+ T cells and plasma cells, has been strongly linked to fetal brain injury. Neutrophilic infiltration of the placenta is classically associated with bacterial infections, like Group B Streptococcus, which can cause meningitis and fetal brain injury. The cellular response in the fetal brain typically associated with perinatal infectious or inflammatory injury reflects activation of

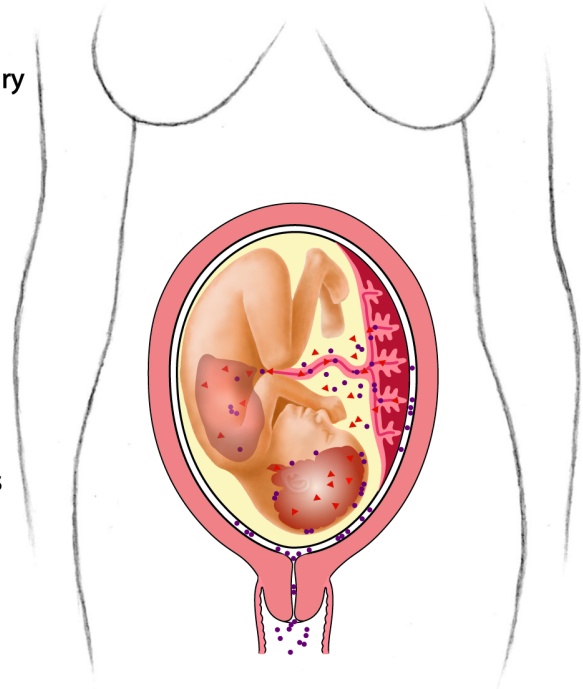
microglia and astrocytes with neuronal loss and oligodendrocyte dysfunction. The pathogens listed are associated with fetal brain injury and in some instances with development of mental illness in the child.

Factors relating perinatal infection to fetal brain injury

- Pathogen virulence
- Pathogen tropism for placenta and fetal brain
- Vertical transmission
- Trimester of exposure
- Duration of infection
- Severity of infection
- Maternal-placental-fetal inflammatory response

Other risk factors for neuropsychiatric disorders

- Genetic predisposition
- Perinatal complications
- Hypoxia

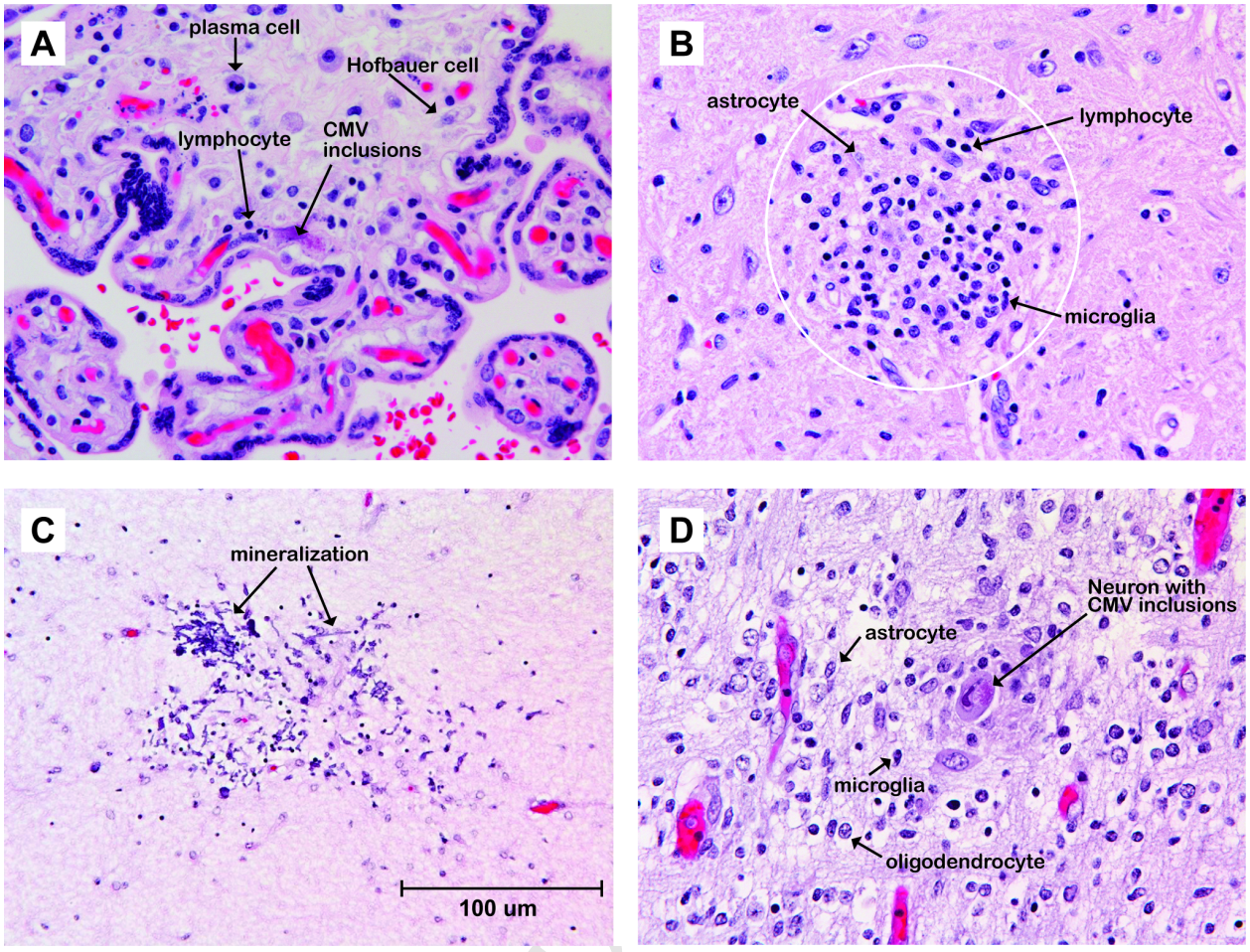


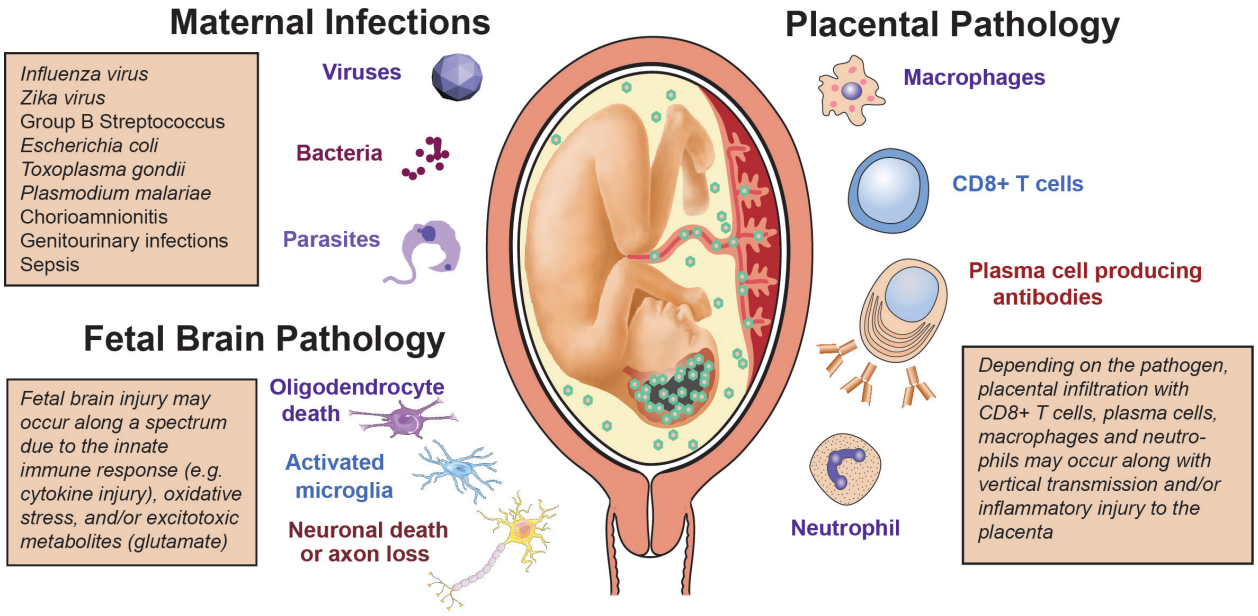
Increased risk for neuropsychiatric and neurodevelopmental disorders

- Autism spectrum disorder
- Schizophrenia
- Depression

Fetal brain injury

- Cognitive deficits
- Social-emotional deficits
- Developmental disability
- Cerebral palsy
- Periventricular leukomalacia
- Ventriculomegaly
- White matter injury
- Microcephaly


A
plasma cell
Hofbauer cell
lymphocyte
CMV inclusions
B
astrocyte
lymphocyte
microglia
C
mineralization
100 um
D
Neuron with CMV inclusions
astrocyte
microglia
oligodendrocyte



Box 1. Clinical and research recommendations

- **Emerging infections**
  - Strengthen public health surveillance for birth defects and long-term adverse outcomes to better determine whether an emerging infectious disease might be teratogenic or result in subtle fetal brain injuries that could predispose to mental illness.
  - Prioritize pregnant women as a high-risk group for efforts to develop acceptable and safe vaccines for use in pregnancy across a spectrum of emerging infections that may be dangerous for pregnancy.
  - Enroll pregnant women in clinical trials to study new vaccines that are anticipated to provide them with benefit (e.g. Zika virus vaccine) at the same time as other study participants and collect information about potential adverse outcomes in pregnancy.
- **Influenza virus infection**
  - Improve uptake of the seasonal influenza vaccine in pregnant women and encourage administration as early as possible once the vaccine is available, including during the first trimester to prevent maternal influenza infections.
  - Educate pregnant women during “influenza season” to notify their provider right away if they have a fever, in order to expedite administration of antiviral therapeutics and supportive care.
- **Preterm labor and intra-amniotic infection**
  - Perform amniocentesis in women presenting with early preterm labor to better evaluate the risk for amniotic fluid infection and need for antimicrobial therapy.
- **Urinary tract infection**
  - Screen women at risk for genitourinary infections with a urine culture once per trimester. Higher risk individuals include women taking immunosuppressive medications or with autoimmune disease (e.g. systemic lupus erythematosus), sickle cell disease, urinary retention,

anatomical urinary tract abnormalities, recurrent urinary tract infections or diabetes.

Box 2. Future research directions

- **Epidemiology and policy**
    - What are the barriers to investigating the link between pregnancy infections, complications, fetal brain injury, birth defects and a long-term increased risk of mental illness for the child?
    - What are the barriers to improving seasonal influenza vaccine uptake in pregnant women around the world?
    - How might improved prenatal care in low income countries reduce long-term burden of psychiatric disease?
- **Pathobiology and the maternal-fetal immune response**
    - What are the risks posed by emerging infectious diseases to the long-term mental health of the child when an infectious exposure occurs during pregnancy?
    - Can emerging infectious diseases penetrate placental defenses?
    - What are the placental and fetal immune correlates of fetal brain injury that predispose to a long-term risk of mental illness?
    - Is there a gestational age window of greatest susceptibility to fetal brain injury?
    - Is there a differential risk for fetal brain injury depending upon fetal sex?
- **Antimicrobial therapeutics**
    - What is the relationship between the use of antibiotics and the fetal inflammatory response? Is this relationship dependent upon the class and type of antibiotic used? How does antibiotic administration timing in relation to infection onset alter inflammatory response?
- **Preterm labor and intra-amniotic infection**
    - Can amniocentesis or vaginal/cervical point of care tests be used to better identify pregnancies with an intra-amniotic infection that might benefit from antibiotics?
    - In the context of an intra-amniotic infection, can fetal brain injury and the long-term risk of mental illness in the child be mitigated by the use of anti-inflammatory therapies in conjunction with antibiotics?

- **Urinary tract infection**
    - Does a maternal urinary tract infection result in a regional inflammatory response that imparts a higher risk for subtle fetal brain injury and long-term risk of mental illness?
    - Does screening pregnant women at high-risk for recurrent urinary tract infections mitigate the long-term increased risk of mental illness for the fetus?