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Beyond TORCH: A narrative review of the impact of antenatal and perinatal infections on the risk of disability

Monica Devaraju[a,b,*], **Amanda Li**[b,c,*], **Sandy Ha**[b], **Miranda Li**[a,b], **Megana Shivakumar**[b], **Hanning Li**[b], **Erika Phelps Nishiguchi**[d], **Patrick Gérardin**[e,f], **Kristina Adams Waldorf**[b,#], **Benjamin J.S. al-Haddad**[g,h,#]

[a]University of Washington, School of Medicine, 1959 NE Pacific St, Seattle, WA 98195, USA

[b]University of Washington, Department of Obstetrics, 1959 NE Pacific St, Seattle, WA 98195, USA

[c]Case Western Reserve University, 10900 Euclid Ave, Cleveland, Ohio, USA.

[d]University of Hawaii, Department of Pediatrics, Division of Community Pediatrics, 1319 Punahou St, Honolulu, Hawaii, USA.

[e]INSERM CIC1410, Centre Hospitalier Universitaire de la Réunion, Saint Pierre, Réunion, France

[f]Platform for Clinical and Translational Research, Centre Hospitalier Universitaire, Saint Pierre, Réunion, France

[g]University of Minnesota, Department of Pediatrics, Division of Neonatology, Academic Office Building, 2450 Riverside Ave S AO-401, Minneapolis, MN 55454

[h]Masonic Institute for the Developing Brain, 2025 E River Pkwy, Minneapolis, MN 55414

Abstract

Infections and inflammation during pregnancy or early life can alter child neurodevelopment and increase the risk for structural brain abnormalities and mental health disorders. There is strong evidence that TORCH infections (i.e., *Treponema pallidum, Toxoplasma gondii*, rubella

[#]**Co-Corresponding Authors:** Benjamin J.S. al-Haddad, haddad@umn.edu, Fax: (612) 624-8176; University of Minnesota, Department of Pediatrics, Division of Neonatology, Academic Office Building, 2450 Riverside Ave S AO-401, Minneapolis, MN 55454, USA; Kristina Adams Waldorf, adamsk@uw.edu, University of Washington, PO Box 358070, 750 Republican Street, Seattle, WA 98109, USA.

[*]Equal contribution

Author Contributions

Conceptualization: M.D., A.L., K.A.W, B.J.S.H.

Methodology: M.D.; A.L.; K.A.W; B.J.S.H.

Writing – Original Draft Preparation: M.D., A.L., S.H., M.L., M.S., V.L., E.P.N., P.G., K.A.W, B.J.S.H.

Writing – Review & Editing: M.D., A.L., S.H., M.L., M.S., V.L., E.P.N., P.G., K.A.W, B.J.S.H.

Supervision: K.A.W; B.J.S.H.

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virus, cytomegalovirus, herpes virus) alter fetal neurodevelopment across multiple developmental domains and contribute to motor and cognitive disabilities. However, the impact of a broader range of viral and bacterial infections on fetal development and disability is less well understood. We performed a literature review of human studies to identify gaps in the link between maternal infections, inflammation, and several neurodevelopmental domains. We found strong and moderate evidence respectively for a higher risk of motor and cognitive delays and disabilities in offspring exposed to a range of non-TORCH pathogens during fetal life. In contrast, there is little evidence for an increased risk of language and sensory disabilities. While guidelines for TORCH infection prevention during pregnancy are common, further consideration for prevention of non-TORCH infections during pregnancy for fetal neuroprotection may be warranted.

Keywords

neurodevelopment; maternal immune activation; perinatal complications; TORCH infections; sensory disabilities; behavioral disabilities; cognitive and intellectual disability; learning disability; speech language disorders; motor skills disorders; neurodevelopmental delay

Introduction

Brain development is a complex process that begins a few weeks after conception and continues through childhood and adolescence. In fetal life, exposure to inflammatory or infectious agents can perturb or arrest fetal brain programming with major consequences for motor abilities, cognitive function and mental health [1,2]. Strong evidence links “TORCH” infections in the mother during pregnancy to sensory and motor deficits in the child. “TORCH” is a mnemonic which currently stands for *Treponema pallidum* (syphilis), *Toxoplasma gondii*, “other” pathogens [varicella-zoster virus (VZV), parvovirus B19)], rubella virus (RuV), cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis viruses, and human immunodeficiency virus (HIV). Mother-to-child transmission of TORCH pathogens can occur either prenatally, perinatally, or postnatally through breastfeeding, but most often transmission occurs *antepartum* through transplacental passage of organisms. TORCH infections acquired during pregnancy are characterized by complex fetal brain injuries, which can have long-term neurologic effects on the child [3-7] and eventually in the adult. In contrast, the impact of most other “non-TORCH” infections on fetal and child neurodevelopment and neurologic deficits is poorly understood. There is a large body of work examining the risk of prenatal infection on later development of psychiatric pathology over the life course [8-10]. However, in this review, we focus on the question of whether endemic infectious diseases, like malaria, or bacterial infections (e.g., genitourinary infections) can also cause fetal brain injuries that lead to cognitive, motor or other delays or disabilities when acquired by a pregnant individual. For these and other non-TORCH infections, the impact of a maternal infection on child developmental outcomes is not generally appreciated.

The original “TORCH” paradigm was defined in 1971 by Andres Nahmias to capture four congenital infections: TOxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex Virus [11]; the “O” later came to stand for “Other” pathogens that included parvovirus B19 and

the “H” was expanded to include hepatitis B virus [12]. Traditionally, TORCH pathogens have several common characteristics including a mild illness in the infected mother, vertical transmission to the fetus, and a spectrum of several anomalies that develop in the affected fetus [13]. More recently, Zika virus (ZIKV) has also been labeled as a new “TORCH” pathogen [14-17], due to its link with complex neurologic and sensorineural injuries, microcephaly [18], and neurocognitive impairments [19]. However, there are generations within the medical and scientific workforce that associate only the specific pathogens specified by the “T”, “R”, “C”, and “H” letters with congenital anomalies and neurologic impairment. Our current understanding of the complex interactions between maternal infections and fetal/child neurodevelopment extends well beyond this simple paradigm. A broader range of bacterial and viral infections have now been studied in pregnancy with a variable focus on the different neurologic outcomes in the exposed fetus. In this review we sought to determine the spectrum of developmental differences posed by a wide spectrum of “non-TORCH” infections focusing on non-psychiatric pathology.

The objective of our narrative review was to analyze the strength of the evidence in the literature for causal relationships between non-TORCH infections and neurodevelopmental delays and disabilities in the child to highlight pathogens of concern beyond TORCH. We used a developmental domain framework seeking to classify evidence of delay or disability according to functional areas of child development. While there are many developmental frameworks and classification systems, in this review we focus on a child’s motor, cognitive, sensory, and language development.

Adverse Neurologic Outcomes Induced by TORCH Pathogens

An analysis of the adverse outcomes induced by TORCH pathogens represents a starting point for consideration of neurologic outcomes potentially linked to non-TORCH pathogens. Notable clinical symptoms that are characteristic of TORCH infections at birth include fever, jaundice, low birth weight, purpura (small red or brown dots), blue/purple spots (rash), an enlarged liver, and eye injuries or cataracts (Table 1, Figure 1). Among the TORCH pathogens, *T. gondii, T. pallidum*, RuV, CMV, and HSV 1 and 2, HIV and ZIKV are known to increase the risk of motor delay and disability through widespread neurological damage, particularly in the motor cortex [20-25][26,27]. Studies have also established that infants exposed to maternal TORCH infections are at higher risk for cognitive, learning, and speech & language delays and disabilities [23,28-34] [22,35-51]. TORCH infections are also classically linked to eye injuries, such as congenital cataracts and chorioretinitis [52-58]. Auditory development is similarly disturbed by several TORCH infections [59-69]. A range of complex motor, learning, speech, sensory and cognitive deficits are strongly associated with classic TORCH pathogens.

Maternal Immune Activation Hypothesis

Although not specific for any pathogen, there is another paradigm that requires examination when analyzing links between fetal exposure to non-TORCH pathogens and development of neurologic deficits. Many epidemiologic and animal studies suggest that non-TORCH pathogens induce fetal neurologic injury without direct infection of the fetus (Figure 2).

This led to the “maternal immune activation” (MIA) hypothesis which proposed that *in utero* inflammation can alter fetal neurodevelopment through placental transmissions of inflammatory signals between mother and fetus. [70-74] Findings from the animal literature suggest that maternal infection and inflammation can cause generalized changes to white matter and hippocampal development, increased microglial activation as well as alterations in the development of the dopaminergic, glutamatergic, serotonergic and GABAergic neuronal systems [75-85]. Mechanisms causing abnormal oligodendrocyte development and death are also under study [86-89]. Maternal inflammation also appears to induce epigenetic changes through histone acetylation, DNA methylation and microRNA expression in a host of genes [73,90]. Although it is not yet known how maternal infection during particular gestational windows may differentially affect neurologic development, evidence from rat studies suggest that infection at different points in gestation may result in different neurological pathologies [91].

The MIA hypothesis raised the possibility that any infectious or inflammatory condition in the mother might be harmful to the fetal brain. Further, it allowed for the use of pathogen-associated molecular patterns, like bacterial cell wall components (e.g., Lipopolysaccharide or LPS) or viral RNA, to model the impact of common bacterial and viral inflammatory insults in animal models on fetal neurodevelopment. The MIA hypothesis also provided a broader foundation for epidemiologic studies to analyze links between systemic bacterial infections, not thought to infect the fetus, and neuropsychiatric pathology in the child. For example, epidemiological studies have investigated the impact of maternal genitourinary and respiratory infections on the long-term mental health of the child and risk of autism spectrum disorder, schizophrenia, and depression [8-10,92,93]. This framework is valuable because it suggests that a broad range of non-TORCH pathogens may also increase the risk of neurodevelopmental delay and disability.

Methods of Narrative Literature Review

We created a search strategy designed to focus on particular developmental domains rather than on general brain injury. We conducted a literature search through November 2022 using the PubMed database centering on MeSH terms “Language Disorders”, “Speech Disorders”, “Developmental Disabilities”, “Sensation Disorders”, “Intellectual Disability”, “Learning Disabilities”, “Behavioral Disorders”, and “Motor Disorders”. First, we coupled each MeSH term with the phrase “infection” or “inflammation” through the Boolean operator “AND”; next, we coupled these terms with “maternal” or “fetal” or “perinatal” or “pregnancy” or “congenital” using the Boolean operator “AND”. We also used “maternal immune activation” in combination with “cognitive”, “learning”, “language”, “dyslexia”, “dyscalculia”, “dysgraphia”, “hearing”, “vision” and “motor” using the Boolean operator “AND”. We utilized this preliminary search to identify the most prevalent neurodevelopmental conditions within each developmental domain considering primarily human studies (Table 2). Additional papers were added to the review based on references that appeared within each paper as well as using the Pubmed “cited by tool”, which revealed more recent papers. We excluded literature on psychiatric disorders and autism spectrum disorder as our intention was to focus on a set of disabilities and delays within a developmental domain framework rather than recapitulate the evidence

on psychiatric pathology outcomes. We additionally excluded papers written in languages other than English. Our review focused on studies assessing correlations between abnormal neurodevelopment in the child after exposure to TORCH or non-TORCH pathogens during fetal life. As the focus of the review was on non-TORCH infections, inclusion of articles related to TORCH infections represented mainly a comparator.

We considered the body of evidence as strong when there was consistent evidence from epidemiological studies from multiple populations with control for confounding and some evidence of increasing risk with physical proximity to the fetal compartment or severity of the infection as well as support from animal studies. We considered the body of evidence weak when there were few or conflicting epidemiological studies without confounder consideration in the design and inconsistent animal model study findings. We considered the body of evidence as moderate when there were consistent animal model findings and several epidemiological studies with confounding considerations with mostly consistent findings.

Results

Evidence Linking Maternal Non-TORCH Infections with Disabilities in Exposed Children

Strong Evidence – Motor Disabilities

There is compelling evidence from both the human and animal literature that maternal infection may increase risk of motor deficits in offspring [91][98,99]. Considering extra-uterine infections first, there is moderate evidence that prenatal infections including maternal genitourinary tract infection may increase the odds of cerebral palsy (CP) in preterm and low birthweight infants [100]. A Danish population-based study found an increased risk (adjusted HR (aHR), 2.1, 95% Confidence Interval (CI) 1.4 - 3.2) of CP among infants whose mothers were diagnosed with genitourinary tract infection during pregnancy [101]. Another Danish study focusing on self-reported vaginal infections found an increased risk of both CP and spastic CP (aHR 1.52, 95% CI, 1.04 - 2.24; and aHR 1.73, 95% CI, 1.16 - 2.60, respectively), as well as maternal fever and CP (aHR, 1.53; 95% CI, 1.06 - 2.21); however these findings may be subject to significant recall bias [32]. Similarly, a case-control study in Sweden found an increased risk of CP in infants of mothers who had any infection during pregnancy (adjusted odds ratio (aOR) 2.9, 95% CI 1.7 - 4.8), severe infection during pregnancy (aOR 15.4, 95% CI 3.0 - 78.1), bacterial growth in urine during pregnancy (aOR 4.7, 95% CI 1.5 - 15.2), and antibiotic treatment in pregnancy (aOR 6.3, 95% CI 3.0 - 15.2) [104]. In a large cohort of extremely preterm infants in the United States, maternal cervical or vaginal infection during gestation was associated with increased risk of motor delay (aOR 1.7; 95% CI 1.04 - 2.7), though this may be confounded by prematurity [105]. Collectively, there is evidence from both European and U.S. cohorts that a variety of extra-uterine genitourinary infections in pregnancy are associated with an increased risk for development of motor delay and disability.

Among studies considering fetal exposure to bacterial infections or sterile inflammation *in utero*, there appears to be strong evidence for a causal relationship with risk of motor delay and or disability. A clinical or histopathological diagnosis of chorioamnionitis, an acute inflammation of the placental membranes, typically represents a plausible active or resolved polymicrobial bacterial infection that induced a cytokine and chemokine response reaching

the fetus [106-110]. A population-based study in California examined chorioamnionitis in comparison with maternal genitourinary tract and respiratory infections and found a higher odds of CP for the combined clinical and histopathological diagnoses of chorioamnionitis (OR 3.1, 95% CI 2.9 −3.4) than for genitourinary infection (OR 1.4, 95% CI 1.3 – 1.6) and respiratory infection (OR 1.9, 95% CI 1.5 – 2.2) [111]. A meta-analysis of 26 studies found a consistent relationship between chorioamnionitis and risk of CP among full-term infants whose mother was diagnosed with clinical chorioamnionitis (RR) 4.7; 95% CI: 1.3 - 16.2) [112]. Assuming a causal role of chorioamnionitis in some proportion of cases of cerebral palsy, a nested a case-control study using a cohort of 231,582 singleton infants estimated that 11% of all cases of CP in singleton births could be attributable to chorioamnionitis [96]. As expected, an intrauterine localized infection in close proximity to the fetus was associated with a greater increase in the risk for CP than for extrauterine infections.

Considering evidence from animal studies, maternal sepsis was shown to alter strength, coordination, function and ability in the offspring in a murine model [94]. Other work in mice has demonstrated that experimentally inducing maternal inflammation with pathogen-associated molecular patterns [poly(I:C)] to mimic an infection causes motor activity and coordination deficits that seem to be more pronounced in male offspring [95]. Like the mouse model, rabbits exposed to *in utero* LPS had injury to both white and gray matter as well as impaired locomotion and motor deficits related to posture and feeding [96,97].

In contrast to gross motor delay and disability, there is no consistent evidence that maternal infection during gestation increases the risk of repetitive and involuntary movement disorders like Tourette syndrome or other tic disorders. While a small case-control study found that exposure to proinflammatory factors (e.g., autoimmune disease, prenatal infection) was more prevalent in mothers of children with tic disorders [113], other studies have not found a consistent association between maternal infection and tic disorders [114-116]. A large cohort study in Sweden revealed a 60% increase in hazard ratio for developing Tourette syndrome and chronic tic disorder in children exposed to prenatal maternal infection (aHR, 1.60; 95% CI, 1.23 - 2.09); however this relationship was not seen in a sibling-matched sub-analysis suggesting that heritable factors may have a causal role in both risk of tic disorders and infection [117].

Moderate Evidence – Cognitive Disabilities

Considering generalized non-TORCH infections, there is evidence from human studies that maternal infection may increase the risk of child cognitive delay and intellectual disability. Ecological studies have found an increased prevalence of intellectual disability in children and adults born during or after peaks of influenza pandemics. Takei et al. found increased risk of an intellectual disability diagnosis among patients born after peak influenza pandemic periods from 1953 to 1980 in England and Wales [130]. In their model, there was a 17% increase in births of what they deemed “mentally handicapped” individuals six months after respective seasonal peaks [130]. Another study found that male military conscripts in Norway born during the 1969-1970 influenza pandemic had reduced intelligence scores in models comparing them with males born before and after [131]. Population data from California also suggested that children of mothers who experienced a

variety of infections during gestation had an increased risk of intellectual disability; this risk was highest with infection in the second trimester [132]. A large cohort study of children exposed to maternal systemic bacterial infection during pregnancy in Massachusetts and Rhode Island were found have lower IQ scores compared to children that weren't exposed [133]. Similarly, another large cohort study of children exposed to maternal infection in utero in the United Kingdom had lower total IQ at 8 years of age compared to children not exposed to infection [134]. However, a recent population-based study in Sweden found that while maternal infection during gestation was an independent predictor of intellectual disability (aHR, 1.37 95%CI 1.23 - 1.51), this relationship was not statistically significant in a sibling model stratified on the nuclear family; this data suggested that some or all of the relationship between maternal infection and intellectual disability may have been related to familial or unmeasured confounders [135]. Conversely, in their bias analyses, the authors also studied the relationship between maternal infection in the year preceding pregnancy as a negative control and risk of intellectual disability in the child and found no statistical association [135]. Overall, the findings from this important study imply that some degree of unmeasured confounding may influence the apparent relationship between maternal infection and intellectual disability.

Evidence from maternal serum and fetal tissue reflecting systemic inflammatory responses aligns well with both animal and epidemiologic studies suggesting that maternal inflammation imparts a higher risk for child cognitive developmental delay. Several studies have found correlations between maternal inflammatory cytokines like Interleukin-6 and C-reactive Protein during pregnancy and changes in the child's brain structural development, working memory and cognitive scores [136-138]. In a secondary analysis of a country-wide longitudinal cohort study in the United States, funisitis (inflammation of the umbilical cord) was also associated with lower intelligence quotient scores at 4 and 7 years of age [139]. Funisitis and infection of the placenta are closely linked pathologic events during an intrauterine infection.

Maternal urinary tract infections (UTI) have also been regarded as a potentially important source of inflammation during pregnancy. In the Collaborative Perinatal Project which enrolled pregnant women across the United States, follow-up studies found that among white mothers (in contrast with black mothers) UTI during pregnancy increased risk of intellectual disability by 62% in an unadjusted analysis [140]. Langridge et al. also found an increased risk of mild-to-moderate intellectual disability among children of mothers with UTI during pregnancy in Western Australia in an unadjusted analysis [141]. Evidence from a study using public insurance claims data in the United States found similar results with infants of women diagnosed with a UTI who did not take antibiotics having increased risk of intellectual disability or developmental delay (aRR 1.31, 95% CI 1.12 - 1.54) compared to women not diagnosed with UTI and compared to women diagnosed with a UTI who completed an antibiotic course (aRR 1.22 95% CI 1.02 - 1.46) [142]. A similar but unadjusted study in South Carolina had comparable results [143].

Studies in animal models support the detrimental effects of maternal immune activation on offspring cognition and memory [118,119]. Mice exposed to MIA with inflammatory antigens were found to have cognitive impairment related to disruption in the

catecholaminergic, GABAergic and dopaminergic systems [120-124]. Rats with similar inflammatory prenatal exposure had differences in working memory and other cognitive domains compared to non-exposed rats [125-129]. Another study among pregnant rhesus monkeys injected with viral antigen found decreased brain size and cognitive alterations [118].

Lastly, while learning and cognition are difficult to separate, many animal studies have focused on learning deficits after *in utero* exposure to MIA. Learning deficits have been observed in mice and rats exposed to bacterial infections, LPS and viral mimics in-utero [94,125,144,145]. Some work has focused on the possibility of immunologic mediated risk of dyslexia. Vincent et al. injected sera from mothers with multiple children with dyslexia into pregnant mice and found resulting worse performance of mouse offspring on spatial coordination tasks and suggested that this was due to maternal antibodies [146]. In humans, studies into prenatal risk factors for dyslexia date back to the 1950s but have produced little suggestive published evidence [147]. Some epidemiologic evidence from China susceptible to a high degree of recall bias suggested that prenatal maternal infection may increase risk of dyslexia [148].

Minimal Evidence – Language and Sensory Disabilities

While there is an abundance of evidence on the increased risk of abnormal communication with maternal immune activation in animal models in line with work examining risk for autism spectrum disorder, there is little evidence that non-TORCH maternal infections increase the risk of speech or language disorders in humans [149-154]. For example, a study examining receptive language ability found no difference in scores between children exposed *in utero* to maternal upper respiratory tract infection compared to those who were not [157]. Conversely, another small retrospective cohort study of infants less than 30 weeks gestation found that histological chorioamnionitis was associated with language disability [158]. A cross-sectional study in France found no increased risk of language delay with prenatal inflammation among a group of preterm infants [99]. A large selection of studies have found that rats exposed to antenatal inflammation have alterations in communication compared to unexposed rats [127,155,156]. Although the complexity of human language is not perfectly recapitulated by studying communication and vocalization patterns in animal models, one can consider vocalization deficits in animals as an early sign of derailed neurodevelopment.

Finally, there is little evidence that exposure to non-TORCH infections during pregnancy increases the risk of sensory disabilities. The most common sensory disability implicated in maternal gestational infection is sensorineural hearing loss (SNHL) of which immune-mediated mechanisms secondary to viral infection as well as local cochlear inflammatory response are responsible for disease [159]. Two small retrospective studies present conflicting results for a link between chorioamnionitis and hearing loss [160,161]. One case-control study from Columbia suggested a possible increased risk of decreased visual or auditory acuity with maternal acute respiratory tract infection in pregnancy [162].

Understudied Impact of Malaria and Chikungunya Virus on Child Neurodevelopment

Malaria is one of several mosquito-borne infectious diseases that can increase risk of both maternal and fetal morbidity and mortality but has a poorly characterized impact on fetal neurodevelopment [163]. Nearly 125 million pregnant individuals reside in tropical and subtropical areas of the world and are susceptible to Malarial infection via the Anopheles mosquito. Despite this global infectious disease threat, malaria in pregnancy still lacks a reliable small animal model [164]. Two cohort studies in Malawi have found no association between maternal malaria and motor skills deficits [165,166], although language development may be impaired [166]. In a prospective study of 493 mother-offspring pairs in Benin, perinatal exposure to malaria, especially with a greater burden of parasites in maternal blood, was independently associated with impaired gross motor development in infants at 1 year of age, but not at 6 years of age, although the association was observed in the crude analysis [167]. In a recent randomized clinical trial conducted in Uganda examining the effect of malaria in pregnancy and chemoprevention regimens on child neurodevelopmental and behavioral outcomes, it was shown that children exposed to malaria in pregnancy had worse cognitive, behavioral, and executive function scores than unexposed controls [168]. Interestingly, it was demonstrated that more effective chemoprevention regimens did not result in better outcomes, possibly implying that more intensive prevention prior to and early in gestation may be more effective.

Over the last two decades, Chikungunya Virus (CHIKV) infection has become the most prevalent alphavirus disease in the world through the geographic expansion of the Aedes mosquito vectors (i.e., *Aedes aegypti* and *Aedes albopictus*) [169]. More recently, CHIKV was found to be the main neurotropic pathogen among children with brain infections for which cerebrospinal fluid was sampled in coastal Kenya, an area where cerebral malaria and bacterial meningitis had declined due to better vector control [170]. CHIKV can cause both neonatal encephalopathy [171] and encephalitis [172] when transmitted perinatally due to antepartum or intrapartum maternal viremia (absolute risk (AR) 22.5%, 95% CI 9.5 - 35.4% among the exposed; AR 47.6%, 95% CI 24.9 - 69.8% among the infected) [169,171-177]. When infection occurs perinatally, long-term neurological sequelae include cerebral palsy, blindness, and seizures [172,175,176].

On Reunion Island, where perinatal transmission of CHIKV was first documented [171], 51 percent of children exposed to perinatal mother-to-child CHIKV infection had global neurodevelopmental delay at two years of age, (aRR 2.79, 95%CI 1.45 - 3.02) compared to uninfected controls in a model adjusted for maternal social status, gestational age, small for gestational age and head circumference [176]. Specific cognitive domains affected included coordination, language, social, and to a lesser extent, gross motor, and postural abilities. Children with encephalopathy or encephalitis exhibited far lower scores across domains than children with milder neonatal disease. Postnatal microcephaly and cerebral palsy were also documented, suggesting that perinatal transmission of CHIKV shares features with classical TORCH pathogens [176]. Given the importance of preventing intrapartum infection with CHIKV, and likely malaria, there is a strong need for vaccines and pharmacotherapeutics which can block the perinatal transmission of these pathogens to the fetus and prevent severe lifelong brain damage.

Knowledge Gaps

The impact of non-TORCH infections on child development is greatly understudied and several systematic reviews are needed that focus on specific developmental domains that include evidence from both TORCH and non-TORCH infections. Although the impact of malaria and CHIKV exposure in utero on child neurodevelopment is a major knowledge gap in the field, there are many other pathogens that may adversely impact fetal neurodevelopment which are currently unknown. Studying the impact of a broad range of bacterial infections at different bodily sites and across a wide spectrum of disease severity is extremely challenging even in countries with national health databases containing decades of data. It also becomes difficult to study the impact of perinatal exposure to a viral or parasitic disease on child development when it becomes endemic in large parts of the world. Although hundreds of millions of pregnant individuals are at risk for acquiring the disease annually, many of these women were exposed once or repeatedly to the pathogen from a young age resulting in partial or protective immunity. Complex host responses to a pathogen can make the impact of the pathogen on the pregnant woman and her child more challenging to study, as it is unclear which individuals are truly susceptible and at greater risk for disease or transmission to the fetus. Further, public health investment in research typically decreases once a pathogen transitions from a pandemic/epidemic to endemic status and it becomes more difficult to set up expensive cohorts of exposed children that will require complex developmental domain testing over many years. Overall, determining the impact of a perinatal exposure to a pathogen on child development is expensive and requires investment in infrastructure to follow the children long-term.

Conclusions

TORCH infections are an important cause of disability worldwide across multiple developmental domains. However, there is strong suggestive evidence that non-TORCH infections during pregnancy may also increase the risk of motor delay and disability. We find moderate evidence that fetal exposure to maternal non-TORCH infections increases risk of cognitive delay and disability in the child. Except for perinatally acquired CHIKV encephalopathy/encephalitis, we find very little evidence for a causal relationship between non-TORCH maternal infections (including malaria) and speech and language and sensory disabilities. Larger, well-designed studies of whether and how malaria or CHIKV during pregnancy may affect neurodevelopment are needed. Further, research into the role of genitourinary tract infections in pregnancy would clarify the importance of these infections for fetal development. Information systems that align data from pregnancy care and pediatric developmental surveillance with new and reemerging pathogens would greatly facilitate long-term studies of neurodevelopmental effects of infection during pregnancy. Lastly, pathogen avoidance and vaccine administration continue to be cornerstones of infection prevention during pregnancy.

With the possible increased risk for global impairments in fetal and child neurodevelopment, prevention of infection during pregnancy continues to be crucial for pregnant women and their infants. While the role of malaria in gestation and subsequent neurodevelopment remains unclear, continued attention to improving coverage of prevention measures like

intermittent prophylaxis, Anopheles mosquito reduction and bed nets [178] are essential. Although a malaria vaccine for use in pregnancy is not yet available, other infections and their sequelae can be prevented during pregnancy [179-181]. For CHIKV, the mechanism of mother-to-child perinatal transmission to the fetus remains elusive and a safe vaccine for pregnant women or immunotherapy protocols during labor or soon after birth are needed [182]. There is growing early evidence but still no consensus on whether infection with SARS-Cov2 during pregnancy increases risk of developmental delay in the child [183,184]. However, given the known increased risk of pregnancy complications for both influenza and SARS-COV2 during pregnancy and the availability of safe and effective vaccines, recommendations for continued vaccination and infection prevention measures for pregnant persons is warranted.

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Abbreviations:

CHIKV	chikungunya virus
CMV	cytomegalovirus
CP	cerebral palsy
HIV	human immunodeficiency virus
HR	Hazard Ratio
HSV	herpes simplex virus
LPS	lipopolysaccharide
OR	Odds Ratio
RR	Risk Ratio
TORCH	Toxoplasma, “Other” (Zika, Varicella, Parvovirus B19), Rubella, Cytomegalovirus, Herpes simplex virus

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Highlights

- We reviewed the evidence for fetal exposure to non-TORCH maternal infections and inflammation on the motor, cognitive, language and sensory developmental domains.
- We found strong evidence for increased risk of motor delay and disability after exposure to non- TORCH maternal infection or inflammation in utero.
- We also found moderate evidence for increased risk of cognitive delay after non-TORCH maternal infection or inflammation in utero.
- There was little evidence for increased risk of language or sensory disability.

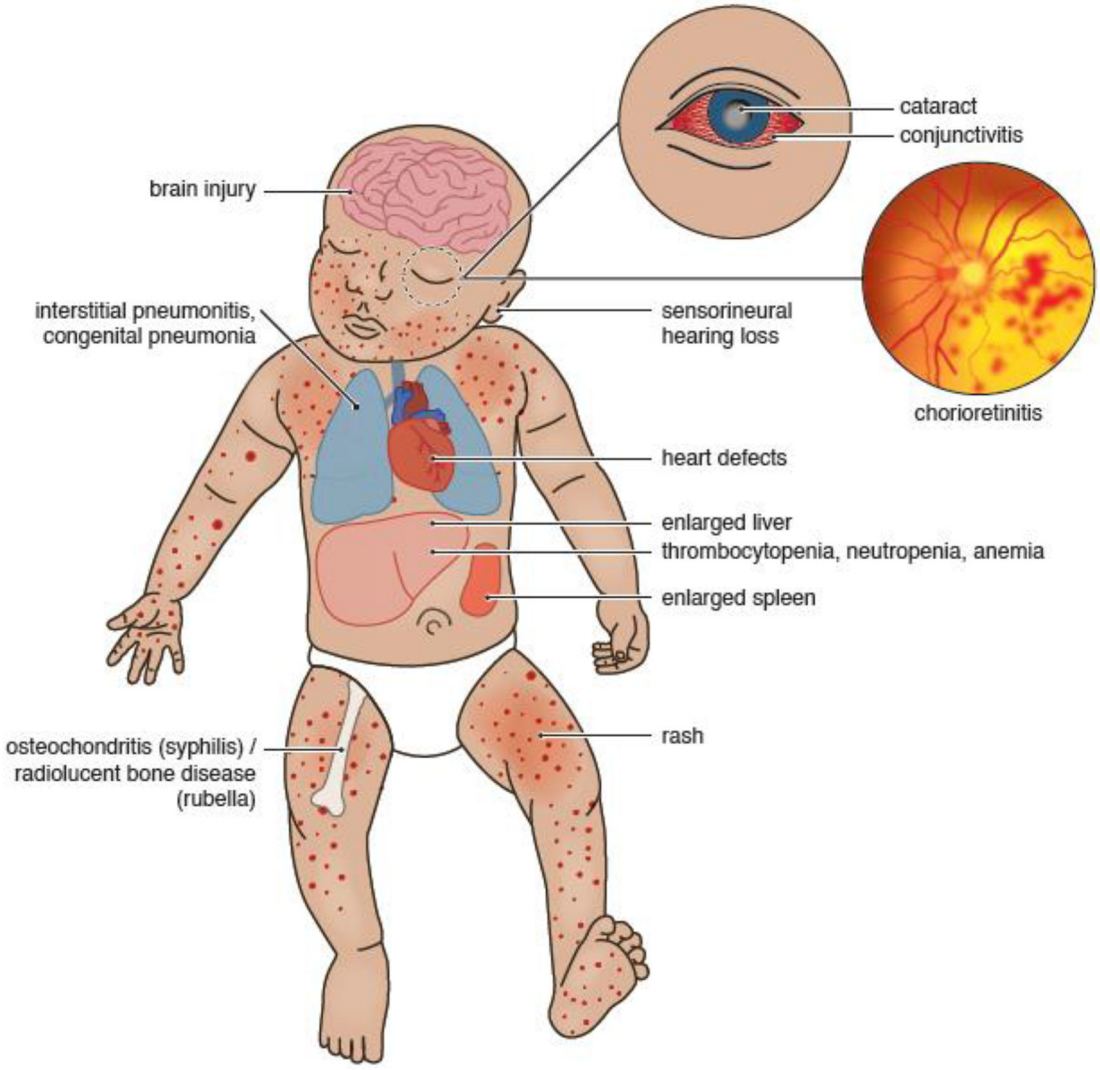

Figure 1. Neonatal Outcomes Associated with TORCH infections.

This figure illustrates the neonatal clinical findings associated with TORCH infections during pregnancy. TORCH infections in pregnancy are typically associated with a spectrum of congenital anomalies including congenital brain injuries, heart defects, sensorineural hearing loss, hepatosplenomegaly, liver dysfunction, conjunctivitis, chorioretinitis, lung inflammation and infection.

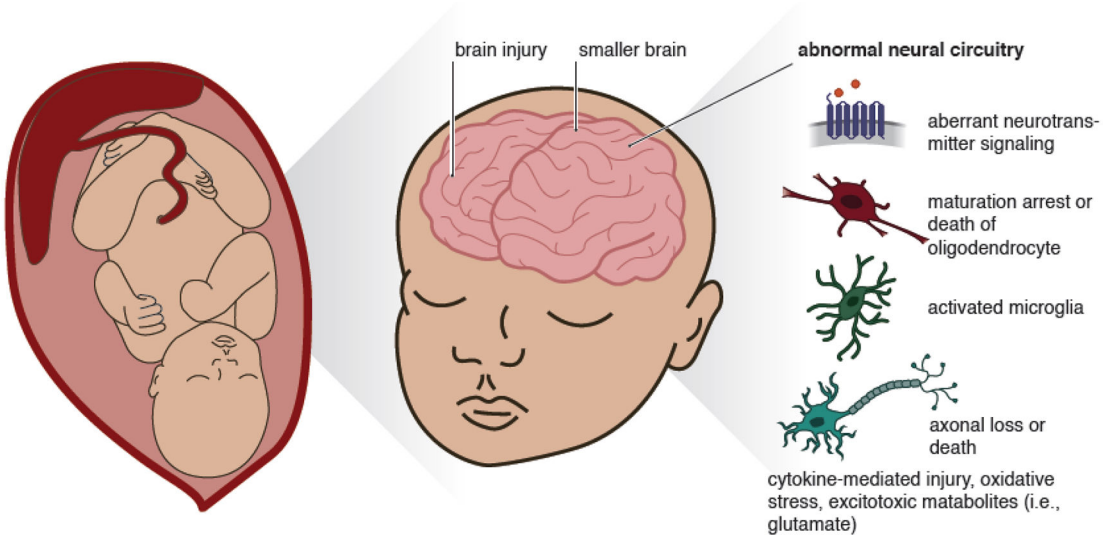

Figure 2. Fetal Brain Injury in Response to Non-TORCH pathogens.

This figure illustrates some of the mechanisms through which maternal infections caused by “non-TORCH” pathogens may alter fetal brain development. Fetal brain changes may be mediated through aberrant neurotransmitter signaling, abnormal growth or death of oligodendrocytes, microglial activation, direct neuronal injury or death from cytokines, oxidative stress, and toxic metabolites.

Table 1.

TORCH Pathogens, Transmission Temporality, and Neonatal Outcomes

TORCH Letter	Pathogen (disease)	Transmission temporality	Strong clinical correlates of disease in neonate
T	*Toxoplasma gondii* (toxoplasmosis)	Greatest risk for congenital anomalies with a maternal third trimester infection	Intra-uterine growth restriction, jaundice, diffuse intracranial/intraparenchymal calcifications, chorioretinitis, hepatosplenomegaly, petechiae/ purpura, chorioretinitis
T	*Treponema pallidum* (syphilis)	Greater risk of congenital disease with acquisition in 2nd trimester or later	Thrombocytopenia, maculopapular rash on palms & soles, Hutchinson's teeth, hydrocephalus, hepatosplenomegaly, petechiae/ purpura, chorioretinitis
O	Parvovirus B19 (Fifth's Disease)	Greater risk of fetal anemia and non-immune hydrops in the 2nd trimester. Fetal acquisition of infection ~1-3 weeks after maternal infection.	Subcutaneous edema, hydrops fetalis, myocarditis & heart failure, retinal and corneal abnormalities, hepatosplenomegaly, petechiae/ purpura, chorioretinitis
O	Zika virus (Congenital Zika syndrome)	Vertical transmission and fetal microcephaly can occur with maternal infection in any trimester	Newest "TORCH" pathogen due to complex and severe neurological injuries of the fetus
R	Rubella virus (Congenital Rubella Syndrome)	Greatest risk with first trimester infection, decreasing risk of vertical transmission as gestation progresses	Sensorineural hearing loss, cataracts, patent ductus arteriosus, pulmonary artery stenosis, myocarditis, microphthalmia, glaucoma, "blueberry muffin rash," hepatosplenomegaly, thrombocytopenia, petechiae/purpura
C	Cytomegalovirus	Equal risk for congenital anomalies with maternal infection in any trimester Greater risk of congenital disease with primary infection as opposed to reactivation	Microcephaly, periventricular calcifications, sensorineural deafness, Hepatosplenomegaly, petechiae/purpura, chorioretinitis
H	Herpes virus simplex	Worst outcomes linked to perinatal acquisition at the time of birth. Greater risk of congenital disease with primary infection as opposed to reactivation	Skin-eye-mucus membrane lesions, fever, vesicular rash, meningoencephalitis, myocarditis, cataracts, hepatosplenomegaly, petechiae/purpura, chorioretinitis

This table shows the connection between commonly associated "TORCH" pathogens, risk for vertical transmission depending on the time in gestation of maternal infection, and the clinical outcomes observed in the neonate. Abbreviations are shown in the table.

Table 2.

Developmental Domains Analyzed for Injury by Non-TORCH Pathogens or Infections

Developmental Domain	Defining Features	Example Clinical Diagnoses in the Child
Motor	Deficits in movement and coordination, typically diagnosed when difficulty with motor skills affects activities of daily living	Cerebral palsy
Intellectual/ Cognitive	Permanent limitations of cognition and intelligence, characterized by deficits in learning, logical reasoning, problem-solving, interpersonal skills, practical skills defined by intelligence quotient of less than 70, or 2 standard deviations below the median.	Cognitive impairment
Learning	Impairments in academic function that are not due to sensory deficits, where difficulty is experienced with reading, writing, or mathematics	Dyslexia, dyscalculia, dysgraphia, nonverbal learning disorders
Communication	Speech Disorders: problems with articulation and fluency when speaking Language Disorders: difficulty comprehending and using spoken or written language (form, content, function)	Speech delay, language delay
Sensory	Disorders affecting somatosensory system (processing information related to vision, hearing, taste, smell and other special senses)	Sensorineural hearing loss, decreased visual acuity

This table shows the definitions of the developmental domains that were assessed for associations with maternal non-TORCH infections. For another developmental domain framework example with age-specific milestones, see [185].