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REVIEW ARTICLE

From decidua to brain: Immune pathways linking maternal infections to neurodevelopmental disorders in offspring

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Abstract

Background: The decidua, a specialised endometrial tissue formed during pregnancy, balances maternal tolerance to the semi-allogeneic fetus with defence against pathogens; maternal infections disrupt this environment, triggering maternal immune activation, placental dysfunction, and adverse fetal neurodevelopment. **Aim:** To compare how human immunodeficiency virus (HIV), Zika virus, and cytomegalovirus (CMV) dysregulate the decidual microenvironment and how these disruptions contribute to adverse neurodevelopmental outcomes in offspring. **Methods:** A narrative review of the published literature was conducted, synthesising evidence on pathogen-specific effects on decidual immune regulation, maternal immune activation, placental dysfunction, epigenetic modifications, and neurodevelopmental outcomes. **Results:** HIV predominantly induces chronic systemic inflammation and placental insufficiency; Zika virus directly infects decidual and placental cells to breach the maternal–fetal barrier; and CMV exerts combined cytopathic and inflammatory effects. Despite distinct mechanisms, all three pathogens disrupt the decidual microenvironment and converge on epigenetic reprogramming as a shared molecular pathway linking prenatal immune challenge to persistent neurodevelopmental impairment. **Conclusion:** Comparative evaluation of pathogen-specific mechanisms clarifies how maternal infections influence fetal neurodevelopment and highlights shared and divergent targets for future preventive and therapeutic strategies. **Relevance for patients:** These findings may support earlier prenatal screening, informed clinical management of at-risk pregnancies, and interventions to reduce long-term neurodevelopmental disorders in exposed children.

Keywords: Decidua; Maternal–fetal interface; Human immunodeficiency virus; Zika virus; Cytomegalovirus; Neurodevelopment; Epigenetics

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1. Introduction

The complex interplay between genetics and the cellular environment has fundamentally shaped our understanding of human development and disease. The microenvironment can be defined as the immediate cellular surroundings, including extracellular matrix components, signalling molecules, immune cells and physical factors that collectively influence cell behaviour and function.[1] This environment plays a critical role in regulating gene expression and cellular responses without altering the underlying DNA sequence itself. This complex interaction between genetics and the cellular microenvironment is central to fields such as epigenetics.[2] Epigenetic regulation refers to stable or heritable changes in gene activity or chromatin that occur without changes to the underlying DNA sequence.[2] Such regulation can involve DNA methylation, histone modifications, and non-coding RNA-mediated mechanisms.[2] Epigenetics enables researchers to understand how environmental factors, such as infections, can influence developmental trajectories, disease susceptibility, and phenotypic variation across development and, in some contexts, across generations.[3] Given the well-established link between environmental exposures and neural development, investigating the uterus—the first microenvironment to which all humans are exposed—is essential for understanding how immune pathways can be linked to neurodevelopmental disorders.

2. Literature search strategy

This review employed a narrative, purposive search strategy rather than a systematic protocol. PubMed/MEDLINE and Google Scholar were searched using combinations of terms including "decidua," "maternal-fetal interface," "HIV," "Zika virus," "cytomegalovirus," "maternal immune activation," and "neurodevelopment," supplemented by manual screening of reference lists from key articles. English-language publications from 2005 to 2026 were prioritised, with a small number of older foundational sources retained where directly relevant. Because the search was not conducted according to a pre-registered systematic protocol, this review should be interpreted as a narrative synthesis rather than a comprehensive or exhaustive account of all published literature on this topic.

3. The decidual and maternal–fetal immune microenvironment

3.1. Structure and function of the decidua

The uterus is a pear-shaped, hollow organ found in a woman's pelvis where the prenatal development of a fetus (unborn baby) occurs after fertilisation. Structurally, the uterus has a muscular outer layer, the myometrium, and an inner lining, the endometrium, which transforms into the decidua during pregnancy. The decidua is a transient, specialised tissue that forms the maternal component of the maternal–fetal interface, which is essential for embryo implantation, placental development, and the development and maintenance of maternal–fetal tolerance.[4] It comprises decidual stromal and glandular epithelial cells together with immune cells, including uterine natural killer (uNK) cells and macrophages.[5] The decidual environment balances the seemingly contradictory functions of maintaining immune tolerance to the semi-allogeneic fetus whilst preserving maternal defence against pathogens.[4] Dynamic interactions among decidual stromal cells, uNK cells, macrophages, and regulatory T cells (Tregs) maintain maternal–fetal tolerance while preserving immune surveillance.[6,7]

3.2. Immunological adaptations across pregnancy

3.2.1. Implantation

The decidua initiates the implantation process through a carefully orchestrated pro-inflammatory response. Once the embryo attaches, it triggers a pro-inflammatory response in the decidual stromal cells.[8] These cells secrete cytokines such as interleukin-1 beta (IL-1β), tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and leukaemia inhibitory factor, which recruit innate immune cells, including macrophages, decidual natural killer (dNK) cells, and dendritic cells, all of which are crucial for successful implantation.[8] dNK cells secrete vascular endothelial growth factor and other angiogenic factors, as well as interferon-gamma (IFN-γ), to remodel spiral arteries, ensuring adequate vascular adaptation to support the developing pregnancy.[8] Simultaneously, decidual macrophages clear cellular debris and secrete inflammatory cytokines that promote extracellular matrix breakdown, facilitating trophoblast invasion and progression of implantation.[9] This intricate orchestration of pro-inflammatory signalling and immune cell activity establishes a permissive environment for embryo implantation and subsequent maintenance of pregnancy.

3.2.2. Post-implantation adaptation

Following successful implantation, the uterine microenvironment must adapt from a pro-inflammatory to a tolerogenic state to support the embryo. Decidual stromal cells play a pivotal role in this transition from a pro-inflammatory to a tolerogenic state.[10,11] These cells recruit and induce Tregs by expressing molecules such as human leukocyte antigen (HLA)-G and secreting interleukin-15 and indoleamine 2,3-dioxygenase.[10,12] Indoleamine 2,3-dioxygenase contributes to local immunoregulation

by catalysing tryptophan degradation, thereby helping to suppress T-cell responses, while Tregs expand to suppress maternal effector T cells reactive to paternal antigens.[9,12] The decidual cytokine profile shifts with the suppression of pro-inflammatory cytokines, such as IFN-γ and TNF-α, and an increase in anti-inflammatory cytokines, including interleukin-4, interleukin-10 (IL-10), and transforming growth factor-beta (TGF-β), thereby fostering a tolerogenic decidual milieu.[10] Additionally, trophoblast cells, the outer layer of the blastocyst (early embryo) that forms the placenta, promote vascular remodelling by expressing non-classical major histocompatibility complex (MHC) molecules, HLA-G, HLA-E, and HLA-F, which inhibit uNK cell cytotoxicity while maintaining receptor engagement.[11,13] Immune regulation at the maternal–fetal interface is crucial for maintaining pregnancy and protecting the fetus.

3.3. The maternal–fetal interface

The maternal–fetal interface comprises the fetal placenta and the maternal decidua and functions as both a physical barrier and a bidirectional signalling platform.[14] The decidua directly interacts with invading trophoblasts and produces prostaglandin E2, IL-10, and TGF-β, which help dampen excessive inflammation.[14,15] The syncytiotrophoblast layer lacks classical MHC class I and class II molecules, thereby preventing recognition of maternal T cells and contributing to immune tolerance.[4,15] The maternal–fetal interface also facilitates communication through the secretion of exosomes, microRNAs, and immunosuppressive molecules that modulate maternal immune responses.[16]

During mid- to late pregnancy, immune responses become compartmentalised, maintaining an anti-inflammatory environment at the fetal interface and preserving pro-inflammatory responses in the maternal peripheral immune compartment to combat infections. Decidual macrophages are mainly of an immunoregulatory phenotype, functioning as anti-inflammatory and pro-remodelling effectors.[15] Concurrently, dNK cells remain abundant, ensuring vascular integrity while exhibiting non-cytotoxic activity.[17] This balanced decidual environment must be carefully maintained, as excessive inflammation could lead to miscarriage, preeclampsia, or preterm labour, while inadequate immune responses increase susceptibility to infections.[18]

At term, decidual senescence and inflammatory activation contribute to the initiation of labour. Increased cytokine and chemokine production, together with neutrophil and macrophage infiltration, promotes uterine contractions, cervical ripening, and placental separation; postpartum uterine involution subsequently restores the uterus toward its non-pregnant state.[4,19]

3.4. Maternal infections and disruption of decidual homeostasis

Despite the tolerogenic immune environment, maternal infections during pregnancy can profoundly disrupt the delicate balance at the maternal–fetal interface. Toxoplasmosis; other infections, including human immunodeficiency virus (HIV), syphilis, and parvovirus B19; rubella; cytomegalovirus (CMV); and herpes simplex virus, collectively referred to as TORCH infections, can cause adverse birth outcomes when acquired during pregnancy. Collectively, these infections are associated with intrauterine growth restriction, preterm birth, stillbirth and congenital anomalies affecting multiple organ systems, particularly the developing brain. The mechanisms underlying these adverse outcomes involve maternal immune activation (MIA) characterised by elevated pro-inflammatory cytokines such as IL-6, interleukin-17A (IL-17A), and TNF-α, which alter placental function and interfere with normal fetal neurodevelopment.[20-22]

Congenital infection results from *in utero* transmission from the mother to the fetus. Vertical transmission more broadly may also occur intrapartum or postnatally, depending on the pathogen. These infections may pose substantial risks to long-term neurodevelopment. Congenital transmission occurs when pathogens cross the maternal–fetal interface, either through infection of the placental villous tissue (the functional unit of the placenta containing fetal blood vessels surrounded by trophoblast layers) or via the decidua basalis (the maternal tissue forming the placental bed where maternal blood directly bathes the placental villi).[23,24] This vertical transmission results in direct fetal infection during critical periods of organogenesis and brain development, leading to neurodevelopmental disorders including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability, cerebral palsy, and schizophrenia.[25-27]

4. Mechanistic link between maternal infection and neurodevelopment

4.1. Maternal immune activation

During maternal infection in pregnancy, the mother's immune system mounts a response that extends beyond pathogen clearance to influence fetal development profoundly. The released inflammatory mediators can act at multiple levels: directly at the maternal–fetal interface, by altering placental function, or by directly affecting the fetal

environment and brain development. This multifaceted immune response is termed *maternal immune activation*, a process that has emerged as a critical link between prenatal infection and altered neurodevelopmental trajectories in offspring.[28,29]

Several immune mediators have been identified as critical players linking maternal infection to fetal brain development. IL-6 serves as the central mediator in various MIA models, with placental IL-6 signalling acting as a relay system that transmits maternal inflammation to the fetal brain.[30] Animal studies have demonstrated that maternal IL-6 elevation during pregnancy can alter offspring behaviour, induce anxiety-like phenotypes, and impair social interactions; these behavioural changes resemble ASD-related phenotypes in experimental models.[30] Similarly, the maternal T helper 17 (Th17) cell response and its signature cytokine, IL-17A, have been implicated in abnormal cortical development and behavioural phenotypes. Choi *et al.*[31] demonstrated that maternal Th17 activation and subsequent IL-17A accumulation in the placenta disrupted cortical lamination and induced ASD-like behaviours in offspring by activating specific cortical neurons. Type I interferons, including interferon-alpha (IFN-α) and interferon-beta (IFN-β), possess both antiviral and pro-inflammatory characteristics that can alter placental function and contribute to fetal stress responses.[32] Pro-inflammatory cytokines such as TNF-α and IL-1β further amplify the inflammatory cascade, disrupting trophoblast function and placental integrity.[24] Additionally, maternal antibodies (particularly those targeting fetal brain antigens) can cross the placenta from approximately gestational week 13 and onward and bind to developing neural tissues, potentially interfering with normal neurodevelopmental processes.[29,33]

4.2. Placental mediation of inflammatory signals

The placenta does not act as a passive barrier but as an active sensory and signalling organ that detects, interprets and modulates maternal immune signals. Placental cells express receptors for numerous cytokines and can adapt their signalling responses by amplifying, dampening, or transforming incoming inflammatory signals before relaying them to the fetus.[34] Consequently, maternal inflammation can profoundly alter placental function through multiple mechanisms: reducing nutrient transport capacity, inducing hypoxic conditions, generating oxidative stress and causing localised inflammatory damage to placental tissue.[35] These placental alterations create a compromised intrauterine environment that directly affects fetal nutrient availability, oxygen supply, and exposure to inflammatory mediators, collectively shaping the fetal brain's developmental trajectory.[36]

4.3. Effects on the fetal brain

The developing fetal brain is highly sensitive to inflammatory signals transmitted from the maternal–placental unit. Fetal microglia, which are resident immune cells of the central nervous system (CNS), express receptors for numerous cytokines and are among the first responders to inflammatory signals in the developing brain. Maternal cytokines or placenta-derived inflammatory mediators can induce premature microglial activation, which in turn alters critical neurodevelopmental processes, including phagocytic activity, synaptic pruning, and the release of additional inflammatory mediators.[35,37] Beyond their effects on microglia, inflammatory cytokines can directly reduce neural progenitor cell proliferation, alter neuronal differentiation trajectories, and impair neuronal migration.[36] These processes are essential for appropriate cortical lamination and brain structure formation. Animal studies have consistently indicated decreased neurogenesis, altered cortical layering and disrupted regional brain organisation following MIA exposure.[36]

At the synaptic level, MIA can alter the expression of synaptic proteins, disrupt the excitatory/inhibitory balance critical for neural circuit function, and impair long-term synaptic plasticity. These changes have been directly linked to changes in behavioural phenotypes, including social deficits, repetitive behaviours, and cognitive impairments.[38,39] Placental dysfunction induced by maternal inflammation can cause fetal hypoxia or nutrient restriction, activating hypoxia-inducible factor pathways, which further disrupt brain development by altering angiogenesis, metabolism, and cell survival signaling.[35,36] Some maternal autoantibodies have been found to cross the placental barrier and bind directly to fetal neuronal proteins (including contactin-associated protein 2 and contactin-associated protein-like 2), thereby perturbing normal neurodevelopmental processes.[29,33]

4.4. Epigenetic mechanisms linking prenatal infection to long-term outcomes

Critically, maternal infection during pregnancy can influence fetal neural development not only through direct cytokine signalling and placental dysfunction but also via epigenetic reprogramming. Epigenetic reprogramming provides a molecular mechanism by which transient environmental exposures can produce lasting developmental consequences. Epigenetics, as previously defined, refers to heritable changes in gene expression that occur without alterations to the DNA sequence itself. This is mediated by mechanisms including DNA methylation, histone modifications, and non-coding RNA regulation.[40] Pro-inflammatory cytokines elevated during MIA, including IL-6, IL-1β, and IL-17A, can induce

epigenetic alterations in DNA methylation patterns, histone modifications, and microRNA expression in both placental and fetal neural tissues.[40,41] These epigenetic changes affect the transcription of genes critical for neurogenesis, synaptic formation, neuronal migration, and glial development, resulting in enduring alterations to brain circuitry that persist long after the initial inflammatory insult has resolved.[42,43]

Importantly, such epigenetic modifications are heritable at the cellular level, meaning they are maintained through cell divisions and can persist throughout the lifespan, providing a mechanistic explanation for how transient maternal infection can produce enduring neurodevelopmental vulnerabilities in the offspring.[40,44] These persistent epigenetic changes have been linked to increased susceptibility to neuropsychiatric disorders, including ASD, schizophrenia, ADHD, and mood disorders.[28,33] The epigenetic landscape thus serves as a critical interface between the prenatal environment and long-term neurodevelopmental outcomes, recording and perpetuating the molecular signature of early-life immune challenges.

The maternal–fetal dialogue established following implantation and decidualisation provides the developmental context in which prenatal infections can exert their effects.[45,46] When viral infections such as HIV, Zika virus, or CMV breach this carefully regulated environment, they disrupt multiple levels of this developmental cascade: infecting decidual and placental cells, triggering MIA with its associated cytokine storm, inducing epigenetic reprogramming, and, in cases of congenital transmission, directly infecting fetal tissues, including the developing brain.[47] These multilayered disruptions converge to alter critical neurodevelopmental processes, from neural progenitor proliferation and neuronal migration during early brain formation to synaptic refinement and circuit maturation in later gestation, ultimately manifesting as a spectrum of neuropsychiatric disorders and neurodevelopmental disabilities.[48] The clinical phenotypes observed in affected children, including intellectual disability, ASD, ADHD, cerebral palsy, epilepsy, and sensory impairments, represent the downstream consequences of these prenatal perturbations, highlighting the profound and lasting impact of maternal–fetal infection on the trajectory of human brain development.[49]

5. Pathogen-specific mechanisms of decidual disruption

5.1. Human immunodeficiency virus

Human immunodeficiency virus infection establishes a state of chronic, systemic immune activation and inflammation in the maternal host that fundamentally alters the immunological landscape of pregnancy. Viral replication triggers the release of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, by infected and activated immune cells throughout the body, including the uterine microenvironment (Figure 1). The decidua, which under physiological conditions maintains a carefully balanced anti-inflammatory and tolerogenic milieu essential for embryo implantation and placental development, is exposed to elevated pro-inflammatory signaling.[15,24] This inflammatory transformation creates a pro-inflammatory environment that compromises the decidual capacity to support implantation, placental development, and maternal–fetal tolerance, while simultaneously inducing dysregulation of decidual immune cell populations critical for pregnancy maintenance.[15,50]

5.1.1. Immune dysregulation at the maternal–fetal interface

Under normal pregnancy conditions, uNK cells support vascular remodelling by producing growth factors, as previously described. However, in the context of HIV infection, uNK cells undergo functional reprogramming and become dysfunctional. The cells shift from their supportive, angiogenic phenotype to a pro-inflammatory state characterised by increased production of IFN-γ and other inflammatory cytokines, rather than growth factors.[51,52] This phenotypic shift inhibits the critical process of spiral artery remodelling, potentially leading to inadequate uteroplacental blood flow, placental hypoxia and placental insufficiency, conditions associated with growth restriction and adverse pregnancy outcomes.[52,53]

Macrophages are myeloid-lineage phagocytic cells found in virtually every tissue of the human body. They serve critical roles in maintaining homeostasis, orchestrating immune responses and facilitating tissue repair. These cells exhibit remarkable functional plasticity, capable of adopting distinct phenotypes in response to local environmental cues.[7,15] In normal pregnancy, decidual macrophages predominantly exist in an alternatively activated M2-like tolerogenic state, characterised by the expression of anti-inflammatory cytokines (IL-10, TGF-β), the promotion of tissue remodelling and angiogenesis, and the suppression of inflammatory responses, functions essential for supporting implantation and placental development.[51] However, in HIV infection, the chronic inflammatory environment drives macrophage polarisation toward a classically activated M1-like pro-inflammatory state, characterised by production of inflammatory cytokines (TNF-α, IL-1β, IL-6), reactive oxygen species, and nitric oxide that can cause tissue damage and amplify local inflammation.[54-56]

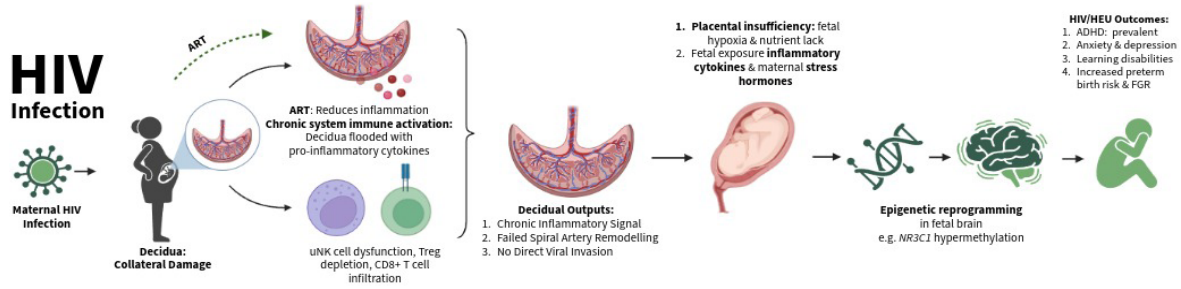


Figure 1. Impact of maternal human immunodeficiency virus (HIV) Infection on decidual function, placental insufficiency, and neurodevelopmental outcomes in offspring. This schematic depicts the pathogenic pathway triggered by maternal HIV infection during pregnancy and its impact on the decidua, placenta, and fetal neurodevelopment. Maternal HIV infection results in chronic systemic immune activation characterised by a decidual microenvironment flooded with pro-inflammatory cytokines. Despite the use of antiretroviral therapy (ART), dysfunction occurs in uterine natural killer (uNK) cells, regulatory T cell (Treg) depletion, and infiltration of cytotoxic $CD8^+$ T cells, leading to collateral decidual damage. The decidua exhibits chronic inflammation, failed spiral artery remodelling, and no direct viral invasion. These placental insufficiencies expose the fetus to hypoxia, nutrient deprivation, inflammatory cytokines, and maternal stress hormones, resulting in epigenetic reprogramming of the fetal brain (such as NR3C1 hypermethylation) and subsequent neurodevelopmental outcomes. Clinical consequences observed in HIV-infected and HIV-exposed uninfected (HEU) children include increased prevalence of attention-deficit/hyperactivity disorder (ADHD), mood and anxiety disorders, learning disabilities, higher preterm birth risk, and fetal growth restriction (FGR). Created in BioRender. LS. (2026) https://BioRender.com/egic9o3.

This macrophage repolarisation contributes to decidual dysfunction, impaired trophoblast invasion, and increased risk of adverse pregnancy outcomes. Furthermore, decidual macrophages can become infected with HIV, serving as viral reservoirs within the decidual tissue and perpetuating local inflammation.[55,57]

Human immunodeficiency virus directly infects and progressively depletes $CD4^+$ T cells, including Tregs, through viral cytopathic effects and immune-mediated destruction. Tregs are particularly critical in the maternal–fetal interface, where they actively suppress maternal immune responses to fetal antigens.[4,58] HIV infection compromises Treg function and abundance in the decidua through multiple mechanisms. These mechanisms include the direct infection and depletion of $CD4^+$ Tregs, disruption of Treg suppressive capacity due to chronic immune activation and alteration of the cytokine milieu that normally promotes Treg differentiation and expansion.[55,59] When Tregs are functionally impaired or depleted in the decidua, the maternal immune system loses its capacity to suppress anti-fetal immune responses effectively. This increases the risk of immune-mediated pregnancy complications.[15,24]

Simultaneously, the maternal immune response to HIV infection activates and expands cytotoxic $CD8^+$ cells, which recognise and kill virus-infected cells. Under normal pregnancy conditions, cytotoxic $CD8^+$ cells are largely excluded from the decidua to prevent harm to placental tissues that express paternal antigens.[60,61] However, HIV-related chronic inflammation can compromise this protective barrier, allowing activated $CD8^+$ T cells to infiltrate decidual tissue where they can directly kill HIV-infected decidual cells, cause collateral damage to healthy placental and decidual tissue through cytotoxic mediator release, and potentially mount anti-fetal immune responses.[62,63] Moreover, HIV infection causes infected immune cells to traffic from peripheral blood to decidual tissue, establishing local viral reservoirs and creating a self-perpetuating cycle of infection, immune activation, inflammation, and tissue damage at the maternal–fetal interface.[64]

5.1.2. Role of antiretroviral therapy

It is essential to recognise that effective antiretroviral therapy (ART) profoundly alters the impact of HIV on pregnancy by suppressing viral replication and reducing viral load (the quantity of virus detectable in blood and tissues) to undetectable or very low levels. This viral suppression confers substantial benefits for maternal health by reducing systemic immune activation and inflammation, thereby helping to restore or maintain a healthier decidual microenvironment conducive to successful pregnancy. Consistent and early initiation of ART during pregnancy has been demonstrated to improve maternal health outcomes, lower the risk of perinatal HIV transmission to less than 1%–2% in adherent individuals (compared to 15%–45% without intervention), reduce the incidence of pregnancy complications and support healthier overall pregnancy outcomes, as reported by the Joint United Nations Programme on HIV and AIDS (UNAIDS) in 2021. The paradigm shift introduced by widespread ART availability has transformed HIV from a condition with near-certain vertical transmission to one

where mother-to-child transmission is now a preventable outcome in settings with access to care.

5.1.3. Mechanisms of vertical transmission

As previously noted, HIV can be transmitted from mother to child through three distinct routes: *in utero* (transplacental transmission during pregnancy), intrapartum (exposure to infected maternal blood and cervicovaginal secretions during labour and delivery), or postnatally (through breastfeeding). *In utero* transmission, though less common than intrapartum transmission in the absence of interventions, occurs when HIV crosses the placental barrier by infecting placental cell types including syncytiotrophoblasts (the multinucleated outer epithelial layer in direct contact with maternal blood), cytotrophoblasts (trophoblast progenitor cells), villous stromal fibroblasts, and critically, Hofbauer cells, fetal-derived macrophages residing within the placental villous core that serve as important viral reservoirs.[65,66] Once the virus breaches the placental barrier, it can access fetal circulation and potentially infect fetal tissues, including the developing brain, where HIV can directly infect microglia (brain-resident macrophages), astrocytes, and potentially other neural cell types.[24,67]

Unlike Zika virus and CMV, HIV less commonly causes direct infection of fetal neural tissue; its neurodevelopmental effects are thought to arise predominantly through chronic maternal systemic inflammation and secondary placental insufficiency, making it the clearest example among the three pathogens of an indirect, inflammation-driven mechanism.

5.2. Zika virus

Zika virus, a mosquito-borne flavivirus, exhibits distinct tropism for cells within the decidual and placental microenvironments, facilitating vertical transmission to the developing fetus (Figure 2). Following maternal infection, the Zika virus directly targets and infects decidual stromal cells, which, upon infection, become sites of productive viral replication that produce high levels of infectious viral particles.[68,69] This establishes the decidua as a primary site of viral amplification during pregnancy. Beyond decidual stromal cells, decidual macrophages and fetal placental Hofbauer cells may become infected and facilitate viral dissemination across placental tissues.[68,70] Additionally, placental trophoblast cells (both cytotrophoblasts and syncytiotrophoblasts) and placental fibroblasts within the villous stroma are susceptible to Zika virus, which directly compromises placental barrier integrity and facilitates viral access to the fetus.[69,70]

5.2.1. Decidual immune response

Unlike HIV, which triggers a generalised systemic inflammatory response, the decidual immune response to Zika is nuanced, complex, and often ineffective at containing viral replication.[71] The first line of antiviral defence, the local type I interferon response mediated by pattern-recognition receptors that detect viral RNA, appears to be weak, delayed, or actively suppressed by viral immune-evasion mechanisms in decidual and placental tissues.[68,72] This inadequate early interferon response provides the Zika virus with a critical window to establish productive infection within the decidual–placental unit

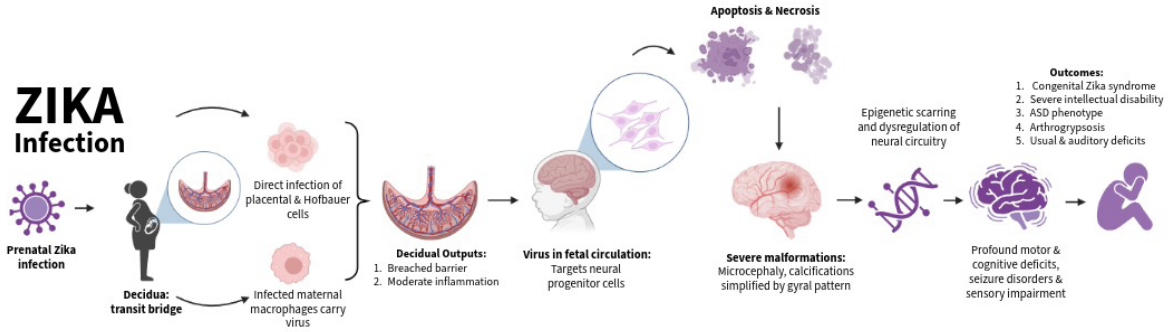


Figure 2. Impact of prenatal Zika virus infection on decidual function, fetal brain development, and neurodevelopmental outcomes. This schematic illustrates the pathogenic cascade initiated by prenatal Zika virus infection and its impact on the maternal–fetal interface and fetal neurodevelopment. Zika virus infects the decidua, with placental trophoblasts and Hofbauer cells as direct targets, while maternal macrophages act as viral carriers crossing the placental barrier. Infection compromises the integrity of the maternal–fetal barrier and moderates inflammation, allowing viral spread into the fetal circulation, where neural progenitor cells become infected. Virus-induced apoptosis and necrosis lead to severe brain malformations, including microcephaly and intracranial calcifications. Epigenetic scarring disrupts neural circuitry, resulting in long-term neurodevelopmental outcomes such as congenital Zika syndrome, intellectual disability, autism spectrum disorder (ASD) phenotypes, arthrogryposis, and sensory deficits. Created in BioRender. LS. (2026) https://BioRender.com/l5jmzyo.

before robust antiviral immunity can be mounted. As innate immune cells detect viral presence, they release pro-inflammatory cytokines, including IFN-α, IFN-β, IL-6, and TNF-α, to control infection.[68,71,73] However, this pro-inflammatory response disrupts trophoblast function, impairs nutrient and oxygen exchange, and contributes to placental insufficiency. Thus, the primary impact of the Zika virus on the decidual–placental unit is twofold: first, it disrupts the protective barrier between mother and fetus by transforming the decidua into a site of active viral replication; and second, it triggers an immune response that, while attempting to control infection, further damages placental integrity and function.[68]

5.2.2. Fetal infection and neurodevelopmental effects

After breaching the placental barrier, Zika virus gains access to fetal circulation. It exhibits strong neurotropism, preferentially targeting and infecting neural progenitor cells, radial glia, and developing neurons within the fetal brain.[74,75] The virus induces direct cytopathic effects, including apoptosis of neural progenitor cells, impaired neurogenesis, disrupted neuronal migration, and abnormal cortical organisation, collectively resulting in severe brain malformations characteristic of congenital Zika syndrome (CZS).[76] Additionally, Zika virus infection triggers activation of fetal microglia and astrocytes, leading to neuroinflammation that further compounds direct viral damage to developing brain tissue.[77,78]

In contrast to HIV's indirect inflammatory route, Zika virus causes the most direct and severe fetal brain injury of the three pathogens, combining decidual/placental barrier breach with strong intrinsic neurotropism, a mechanism that converges partially with CMV's cytopathic tropism but differs in the near-total absence of a protective interferon response.

5.3. Cytomegalovirus

Cytomegalovirus is a beta-herpesvirus that, following primary infection, establishes lifelong latency in the host with periodic reactivation throughout life.[79] During pregnancy, both primary maternal CMV infection and reactivation of latent virus can result in active viral invasion and replication within the decidua and placenta (Figure 3). However, primary infection poses a substantially higher risk for fetal transmission and severe outcomes.[80,81] CMV exhibits broad cellular tropism within the decidual–placental unit, directly infecting decidual stromal cells, uterine glandular epithelial cells, decidual macrophages, uNK cells, and multiple placental cell types, including cytotrophoblasts, syncytiotrophoblasts, villous fibroblasts, and Hofbauer cells.[82,83] This widespread cellular infection compromises both the supportive functions and the immunologically tolerant microenvironment essential for a healthy pregnancy.[84]

Cytomegalovirus infection induces marked cytopathic effects, direct virus-mediated cell damage, in infected decidual and placental cells, characterised by cellular enlargement, intranuclear and intracytoplasmic inclusion

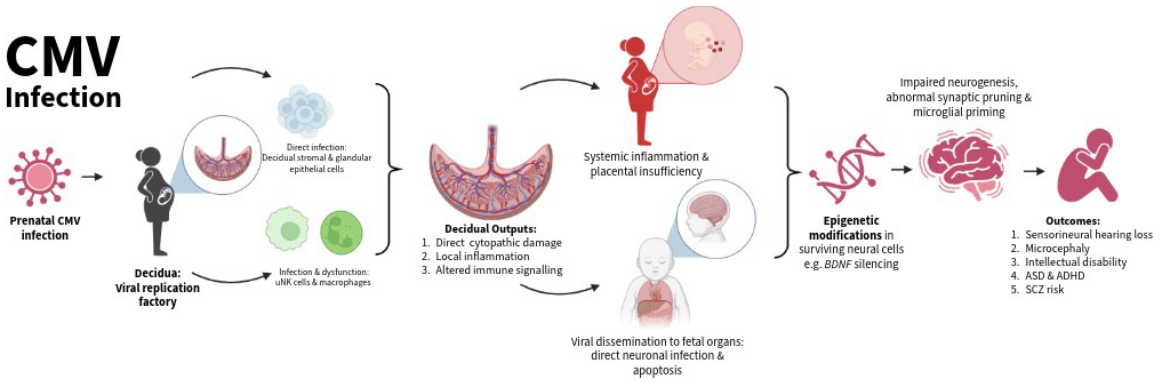


Figure 3. Pathogenesis of prenatal cytomegalovirus (CMV) infection and its impact on decidual function, fetal neural development, and long-term outcomes. This figure illustrates the sequence of events triggered by prenatal CMV infection affecting the maternal–fetal interface and fetal neurodevelopment. Upon maternal CMV infection, the decidua acts as a viral replication factory, with direct infection of decidual stromal and glandular epithelial cells as well as dysfunction of uterine natural killer (uNK) cells and macrophages. These changes lead to local inflammation, direct cytopathic damage, and altered immune signalling within the decidua. The resulting systemic inflammation and placental insufficiency compromise fetal oxygen and nutrient supply, facilitating viral dissemination to fetal organs where direct neuronal infection and apoptosis occur. Epigenetic modifications such as brain-derived neurotrophic factor (*BDNF*) silencing in surviving neural cells contribute to impaired neurogenesis, abnormal synaptic pruning, and microglial priming. This cascade of events culminates in clinical outcomes including sensorineural hearing loss, microcephaly, intellectual disability, increased autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) prevalence, and heightened schizophrenia (SCZ) risk. Created in BioRender. LS. (2026) https://biorender.com/3ejkxn5.

bodies, cell cycle arrest, and eventual cell death.[85] These cytopathic effects, combined with local inflammation and disrupted cellular function, compromise placental development and function, contributing to abnormal spiral artery remodelling, reduced placental perfusion, placental insufficiency, and intrauterine growth restriction.[86,87] Further compounding the disruption, CMV can induce both pro-inflammatory and anti-inflammatory cytokine responses simultaneously, creating an imbalanced and dysfunctional immune signalling environment that is detrimental to normal pregnancy maintenance.[88,89]

5.3.1. Dysregulated immune responses at the maternal–fetal interface

Cytomegalovirus infection fundamentally disrupts the carefully orchestrated immune regulation at the maternal–fetal interface through multiple mechanisms. Infected uNK cells exhibit impaired secretion of angiogenic growth factors (such as vascular endothelial growth factor and placental growth factor) that are essential for spiral artery remodelling and placental vascular development, while simultaneously increasing production of inflammatory cytokines.[90,91] This functional reprogramming of uNK cells compromises placental vascular adaptation and can contribute to placental insufficiency. Concurrently, the pro-inflammatory immune responses triggered by viral detection, including activation of innate immune pattern recognition receptors, production of inflammatory cytokines (TNF-α, IL-6, IL-1β, IFN-γ), and recruitment of additional immune cells, cause collateral damage to the integrity of placental and decidual tissue.[88,92]

Paradoxically, CMV simultaneously induces anti-inflammatory cytokines (such as IL-10 and TGF-β) and employs numerous immune evasion strategies, including downregulation of MHC class I molecules to avoid T cell recognition, expression of viral homologs of immunosuppressive molecules, and inhibition of interferon signalling pathways.[93] This creates a profoundly imbalanced immune signalling environment where inflammatory and anti-inflammatory signals coexist aberrantly, preventing effective viral clearance while simultaneously causing tissue damage, an immunological state fundamentally incompatible with the requirements for healthy pregnancy.[89]

5.3.2. Vertical transmission and fetal infection

Cytomegalovirus crosses the maternal–fetal barrier by infecting and disrupting placental trophoblast cells, and spreads via infected maternal immune cells that traffic to the decidua and placenta.[82,84] Once the virus breaches the placental barrier and enters fetal circulation, it can disseminate widely to fetal organs, with the developing brain being particularly vulnerable.[79] Within the fetal CNS, CMV can infect multiple cell types, including neural progenitor cells, neurons, astrocytes, microglia, and endothelial cells, leading to both direct viral cytopathic damage and inflammation-mediated injury[94] The virus disrupts critical neurodevelopmental processes, including neuronal proliferation, migration, differentiation, synaptogenesis, myelination, and circuit formation, with the specific pattern and severity of damage depending on the timing of infection during gestation and the extent of viral replication in fetal tissues.[79,95]

Cytomegalovirus occupies an intermediate position between HIV and Zika virus: like Zika, it directly infects placental and fetal neural tissue, but like HIV, it also generates a sustained, dysregulated cytokine response. Therefore, combining both mechanisms, rather than relying on either alone, may explain why congenital CMV (cCMV) produces the widest spectrum of severity of outcomes among the three pathogens.

6. Neurodevelopmental and psychiatric outcomes

The evidence for adverse neurodevelopmental outcomes associated with HIV exposure during pregnancy is substantial; however, the underlying mechanisms are complex and multifactorial, involving direct viral effects, chronic MIA, potential ART toxicity, and socioeconomic factors, with some outcomes showing improvement in the era of effective ART.[96] The neurodevelopmental and psychiatric consequences differ markedly between children living with HIV (who acquired infection perinatally) and HIV-exposed uninfected (HEU) children (who were exposed to maternal HIV and often ART *in utero* but did not acquire infection), creating a complex psychiatric landscape that requires separate consideration of these distinct populations.[96,97]

In contrast to HIV, congenital Zika virus infection produces a distinct constellation of congenital abnormalities that was clearly defined during the 2015–2016 epidemic in Brazil and other affected regions. CZS is characterised by a specific pattern of severe anomalies including profound microcephaly (abnormally small head circumference reflecting decreased brain volume), gross brain malformations (such as lissencephaly, ventriculomegaly, and cerebellar hypoplasia), intracranial calcifications (particularly in cortical–subcortical junctions), arthrogryposis (congenital joint contractures), extensive visual impairments (including chorioretinal atrophy, optic nerve abnormalities, and cortical visual impairment), and sensorineural hearing loss.[98–100]

Congenital CMV infection is the most common congenital infection worldwide, affecting approximately 0.4%–0.7% of live births. It is the leading infectious cause of neurodevelopmental disability and sensorineural hearing loss in developed countries.[101] Together, these TORCH infections illustrate diverse pathways to neurodevelopmental and psychiatric morbidity, ranging from direct viral neurotropism and structural brain injury to immune-mediated and treatment-related effects, and provide the framework for the comparative overview that follows.

6.1. Cognitive and intellectual outcomes

6.1.1. Human immunodeficiency virus

Despite effective ART, children living with HIV who acquired infection perinatally remain at risk for neurodevelopmental complications, though the severity has decreased substantially compared to the pre-ART era. Beyond psychiatric diagnoses, children living with HIV frequently exhibit subtle but measurable deficits in processing speed, working memory, executive function, and academic achievement compared to uninfected peers, even when virally suppressed.[102] The neurodevelopmental outcomes of HEU children are a focus of intense research interest, as this population has grown substantially through the successful prevention of mother-to-child transmission and is only now reaching adolescence and young adulthood in sufficient numbers to enable long-term outcome studies.[96]

6.1.2. Zika virus

Long-term psychiatric and neurodevelopmental outcome data for children with CZS are still emerging, as the first cohort of affected children born during the 2015–2016 epidemic is still young and has not yet reached ages when many psychiatric conditions typically manifest.[103] Among children with severe CZS, intellectual disability with associated behavioural disturbances has been consistently documented, with the severity generally correlating with the degree of structural brain abnormality.[104]

6.1.3. Cytomegalovirus

The clinical presentation of cCMV ranges widely in severity. Approximately 10%–15% of congenitally infected infants are symptomatic at birth, presenting with clinical manifestations including microcephaly, intracranial calcifications (particularly periventricular), ventriculomegaly, hepatosplenomegaly, thrombocytopenia, petechiae, jaundice, and sensorineural hearing loss.[105] Among symptomatic infants, 40%–60% will develop significant long-term neurodevelopmental sequelae, including intellectual disability, cerebral palsy, motor deficits, vision impairment (such as chorioretinitis and optic atrophy), and progressive or fluctuating sensorineural hearing loss.[106,107]

6.2. Autism spectrum disorder and attention-deficit/hyperactivity disorder

6.2.1. Human immunodeficiency virus

Children living with HIV on ART demonstrate higher rates of ADHD, which can be attributed to multiple factors, including chronic neuroinflammation (even with viral suppression), direct effects of the virus on brain development, and psychosocial stressors associated with living with a chronic stigmatised condition.[108,109] The most consistent finding across multiple cohort studies is an increased risk of ADHD and attention-related difficulties in HEU children compared to HIV-unexposed children, even after controlling for socioeconomic factors.[110,111] The leading mechanistic hypothesis emphasises that the intrauterine environment of chronic MIA and inflammation, which is characteristic of HIV infection even with viral suppression, affects fetal brain development through the MIA pathways described earlier, including elevated inflammatory cytokines, altered placental function, and epigenetic reprogramming of fetal neural tissues.[96]

6.2.2. Zika virus

The extensive cortical malformations caused by Zika virus infection during critical periods of brain development are hypothesised to represent risk factors for ASD, with initial cohort studies reporting high prevalence rates of autistic features and social-communication impairments in affected children.[112] Similarly, symptoms consistent with ADHD, including impulsivity, hyperactivity, and inattention, have been observed in some affected children. However, formal ADHD diagnoses are difficult to establish in children with severe intellectual disability.[113,114]

6.2.3. Cytomegalovirus

Beyond the well-established risks of intellectual disability, cerebral palsy, and sensory impairments, emerging evidence suggests that cCMV infection may increase risk for neuropsychiatric disorders. Studies have reported increased prevalence of ASD among children with cCMV compared to the general population, potentially reflecting disrupted cortical development, altered synaptic connectivity, and abnormal neural circuit formation resulting from fetal brain infection.[115,116] Similarly, ADHD and associated attention and executive function difficulties have been observed at higher rates in children with cCMV, even among those without frank intellectual disability.[117]

6.3. Motor outcomes

6.3.1. Human immunodeficiency virus

Before widespread ART availability, HIV-infected children frequently developed progressive HIV-associated encephalopathy, characterised by brain atrophy, progressive motor deficits, loss of developmental milestones, and severe cognitive decline.[118,119] In the current ART era, frank encephalopathy has become rare in well-treated children; however, more subtle neurocognitive and neurodevelopmental challenges persist.[120,121]

6.3.2. Zika virus

Congenital Zika syndrome is characterised in part by arthrogryposis (congenital joint contractures).[98-100] Affected infants frequently experience severe motor impairments that reflect widespread CNS damage.[113]

6.3.3. Cytomegalovirus

Long-term sequelae among symptomatic infants include cerebral palsy and motor deficits[106,107]; a subset of infants asymptomatic at birth also go on to develop motor impairments during childhood.[122,123]

6.4. Sensory outcomes (visual and auditory)

6.4.1. Human immunodeficiency virus

Sensory outcomes are not well characterised in the HIV/HEU literature reviewed here and represent a gap relative to the other two pathogens.

6.4.2. Zika virus

Congenital Zika syndrome includes extensive visual impairments (chorioretinal atrophy, optic nerve abnormalities, cortical visual impairment) and sensorineural hearing loss.[98-100] Children without obvious structural abnormalities at birth have nonetheless shown delayed-onset hearing and vision impairments detected during infancy and early childhood.[112] Affected infants frequently experience developmental delays across multiple domains, seizure disorders, feeding difficulties, and severe motor impairments reflecting widespread CNS damage.[113]

6.4.3. Cytomegalovirus

Critically, even the majority (85%–90%) of congenitally infected infants who appear asymptomatic at birth remain at risk for later-onset neurodevelopmental problems, with 10%–15% subsequently developing sensorineural hearing loss (which may be progressive or delayed in onset), learning disabilities, cognitive deficits, motor impairments, or behavioural problems during childhood.[122,123] This finding underscores that the absence of symptoms at birth does not guarantee normal neurodevelopmental outcomes, necessitating long-term audiological and developmental surveillance of all children with confirmed cCMV infection.[107]

6.5. Psychiatric outcomes in adolescence and young adulthood

6.5.1. Human immunodeficiency virus

Among adolescents and young adults living with perinatally acquired HIV, depression and anxiety are commonly reported, influenced by chronic illness burden, social stigma, disclosure challenges, and potential direct effects of HIV-related inflammation on developing neural circuits involved in mood regulation.[124,125] Additionally, secondary psychosis has been reported in cases of poor viral control or advanced disease, likely reflecting direct CNS viral effects and inflammation.[126,127] Emerging studies have also indicated increased risk for mood and anxiety disorders in HEU children and adolescents. However, the relative contributions of prenatal biological factors (MIA, ART exposure) versus postnatal environmental factors (maternal mental health, socioeconomic adversity, stigma) remain under active investigation.[128,129] The specific contributions of *in utero* ART exposure, the maternal inflammatory environment, and psychosocial factors to HEU neurodevelopmental outcomes are critical research questions.[96,130]

6.5.2. Zika virus

Many psychiatric outcomes that typically emerge in middle childhood, adolescence, or early adulthood (such as mood disorders, anxiety disorders, psychotic disorders, and some learning disabilities) cannot yet be fully assessed in this young cohort, meaning the complete psychiatric spectrum associated with CZS remains incompletely characterized.[104,113] Researchers will need to continue longitudinal follow-up as this cohort ages to fully understand the psychiatric consequences of *in utero* Zika virus exposure, particularly for children with more subtle disruptions in neural connectivity who may not have manifested obvious structural brain abnormalities at birth.[104]

6.5.3. Cytomegalovirus

Epidemiological studies have identified associations between maternal CMV infection during pregnancy and increased risk of schizophrenia in offspring, with the hypothesised mechanism involving CMV-induced disruption of fetal brain development during critical windows of cortical organisation and synaptic

formation.[131,132] This association aligns with the broader MIA hypothesis for schizophrenia, whereby prenatal immune challenges, whether infectious or inflammatory, alter neurodevelopmental trajectories in ways that increase vulnerability to psychotic disorders emerging in adolescence or young adulthood.[133]

6.6. Epigenetic mechanisms underlying long-term outcomes

6.6.1. Human immunodeficiency virus

From an epigenetic perspective, studies have begun to identify HIV-associated and ART-associated alterations in DNA methylation patterns in HEU children, particularly in genes involved in immune regulation, neurodevelopment, and stress responses.[134] These epigenetic signatures may represent molecular scars of the prenatal inflammatory environment and could potentially mediate some of the observed neurodevelopmental vulnerabilities, though causative links remain to be definitively established.[135,136]

6.6.2. Zika virus

Additionally, the potential role of epigenetic modifications induced by Zika virus infection in mediating long-term neurodevelopmental outcomes represents an emerging area of investigation, limited in part by the very young age of the current CZS cohort.[137]

6.6.3. Cytomegalovirus

The mechanisms linking cCMV infection to long-term neurodevelopmental and psychiatric outcomes likely involve multiple pathways, including direct viral damage to developing neural tissues, chronic neuroinflammation during critical developmental windows, and epigenetic reprogramming of neural gene expression.[79] CMV infection has been shown to alter DNA methylation patterns, histone modifications, and microRNA expression in infected cells, including neural cells, potentially leading to persistent alterations in gene expression programs governing neurodevelopment, synaptic function, and neural circuit organization.[138] These epigenetic modifications may represent molecular mechanisms by which transient prenatal CMV infection produces lasting effects on brain structure, function, and vulnerability to neuropsychiatric disorders.[94]

7. Comparative synthesis, research gaps, and clinical implications

7.1. Emerging research and clinical implications

7.1.1. Human immunodeficiency virus

Identifying the safest ART regimens for use during pregnancy (those that maximise maternal viral suppression, minimise perinatal transmission, and minimise potential neurodevelopmental toxicity to the developing fetus) remains an important area of ongoing research and clinical guideline development.[139] As the HEU population continues to age, longitudinal studies examining long-term mental health, cognitive trajectories, and functional outcomes into adulthood will be essential for fully understanding the developmental consequences of prenatal HIV exposure in the absence of infection.[140]

7.1.2. Zika virus

The first cohort of children born with CZS remains relatively young, and research is actively tracking their developmental progress, medical needs, quality of life, and life expectancy as they age.[113,141] Critical questions remain under investigation, including why some maternal Zika virus infections lead to severe CZS while others result in milder or no apparent fetal effects; what factors (such as timing of infection, maternal immune response, viral strain, genetic susceptibility) determine disease severity; whether there are critical windows of vulnerability during gestation; and what interventions might mitigate neurodevelopmental damage when maternal infection occurs.[142] Critically, emerging evidence indicates that adverse neurodevelopmental outcomes are not limited to infants with obvious microcephaly at birth. Children who were infected with the Zika virus *in utero* but did not exhibit evident microcephaly or other obvious structural abnormalities at birth have nonetheless shown signs of milder neurodevelopmental delays, behavioural problems, attention difficulties, and delayed onset hearing and vision impairments detected during infancy and early childhood.[112] This finding suggests that the neurodevelopmental impact of congenital Zika virus infection spans a spectrum, with severe CZS representing the most extreme manifestation. Yet, milder neurodevelopmental impairment can occur even in the absence of gross structural brain abnormalities.[143]

7.1.3. Cytomegalovirus

Current research efforts are focused on several critical areas. Longitudinal studies are tracking asymptomatic cCMV-infected infants to better characterise the incidence, timing, and predictors of later-onset neurodevelopmental impairments, particularly cognitive deficits, learning disabilities, and sensorineural hearing loss.[107] Advanced neuroimaging techniques, including magnetic resonance imaging, diffusion tensor imaging, and volumetric brain analysis, are being employed to identify structural brain abnormalities in infected infants that may predict neurodevelopmental risk, enabling earlier intervention.[144,145]

Antiviral treatments, particularly valganciclovir (an oral prodrug of ganciclovir), are being evaluated for efficacy in improving neurodevelopmental outcomes beyond the established benefit for hearing preservation, with ongoing clinical trials assessing optimal dosing, treatment duration, and long-term safety.[122,146] Additionally, research is investigating maternal CMV-specific immunoglobulin therapy to prevent fetal infection after primary maternal infection, developing CMV vaccines to prevent maternal infection during pregnancy, and identifying biomarkers that predict which infected infants are at the highest risk for adverse neurodevelopmental outcomes.[105] Understanding the cellular, molecular, and epigenetic mechanisms by which CMV disrupts fetal brain development will be essential for developing targeted therapeutic strategies to prevent or mitigate the neurodevelopmental consequences of this common congenital infection.[79,94]

7.2. Comparative synthesis

This review has synthesised current evidence demonstrating how HIV, Zika virus, and CMV disrupt the decidual microenvironment through distinct yet overlapping mechanisms, ultimately converging on adverse neurodevelopmental outcomes in offspring. The decidua serves as the critical interface where maternal infections first encounter the developing pregnancy, and the nature of decidual disruption, whether chronic systemic inflammation (HIV), direct viral replication with barrier breach (Zika), or combined cytopathic and immune dysregulation (CMV), determines the subsequent cascade of pathological events affecting fetal brain development. A comparative summary of pathogen-specific maternal–fetal characteristics, mechanisms, and neurodevelopmental outcomes is provided in Table 1.

Human immunodeficiency virus primarily operates through indirect mechanisms, in which chronic MIA increases pro-inflammatory signalling within the decidua, dysregulating decidual immune cell populations (uNK cells, macrophages, Tregs), impairing spiral artery remodelling, and leading to placental insufficiency. This compromised intrauterine environment exposes the developing fetal brain to chronic inflammation, hypoxia, and nutrient restriction, resulting in epigenetic reprogramming that manifests clinically as ADHD, anxiety disorders, learning disabilities, and subtle cognitive impairments, particularly in HEU children. While ART has dramatically reduced vertical transmission and improved outcomes, residual effects of prenatal immune activation persist, highlighting the need for interventions targeting maternal inflammation beyond viral suppression.[147,148]

Zika virus differs mechanistically. Productive infection of decidual and placental cells transforms these tissues into viral replication factories, overwhelming local immune defences and breaching the maternal–fetal barrier. Direct fetal brain infection during critical periods of neurogenesis results in catastrophic neurodevelopmental consequences, profound microcephaly, severe intellectual disability, cortical malformations, and sensory impairments characteristic of CZS. The devastating and irreversible nature of Zika-induced brain damage underscores the urgent need for effective vaccines, vector control strategies, and early diagnostic tools to prevent maternal infection.[68]

Cytomegalovirus occupies an intermediate position, with broad cellular tropism, cytopathic effects, and the paradoxical induction of both pro- and anti-inflammatory responses. This creates a profoundly dysregulated decidual–placental environment that permits viral dissemination to fetal organs while simultaneously damaging the maternal–fetal interface. The resulting spectrum of outcomes, from asymptomatic infection with delayed-onset hearing loss to severe symptomatic disease with multiple neurodevelopmental impairments, reflects the complexity of CMV pathogenesis and highlights the critical need for better risk stratification, antiviral interventions, and long-term developmental surveillance.[82]

Epigenetic modifications emerge as a unifying mechanism linking these diverse infections to persistent neurodevelopmental vulnerabilities. Pro-inflammatory cytokines, placental dysfunction, and direct viral effects converge to epigenetically reprogram fetal neural tissues, altering DNA methylation patterns, histone modifications, and microRNA expression in genes that govern neurogenesis, synaptic formation, and neural circuit organisation. These cellular-level heritable changes provide a molecular explanation for how transient prenatal immune challenges produce lifelong consequences, perpetuating the signature of early-life adversity into childhood, adolescence, and beyond.[44,149]

Monochorionic twin pregnancies offer an instructive non-infectious parallel to the placental-mediated injury described above. Monochorionic diamniotic pregnancies, in which twins share a single placenta with vascular anastomoses, carry substantially higher complication rates than dichorionic twins. This includes twin-to-twin transfusion syndrome, which is associated with increased risk of neurodevelopmental impairment in surviving co-twins.[150] Monochorionic monoamniotic pregnancies carry even greater risk, given the added complication of umbilical cord entanglement, with survivors facing a comparable spectrum of long-term cognitive and motor sequelae.[150] As with HIV, Zika virus, and CMV, the shared thread is disruption at the level of placental vascular

Table 1. Comparative maternal–fetal characteristics and neurodevelopmental outcomes of HIV, Zika virus, and CMV in pregnancy

Characteristic	HIV	Zika virus	CMV
Decidual/placental tropism	Decidual macrophages become infected viral reservoirs; uNK cells and Tregs functionally reprogrammed rather than directly infected[51,55,57]	Decidual stromal cells become sites of productive viral replication; Hofbauer cells/macrophages act as viral carriers across placental layers[68,69,70]	Broad direct tropism: decidual stromal cells, glandular epithelium, uNK cells, macrophages, and multiple trophoblast populations[82,83]
Vertical transmission mechanism	Transplacental infection of syncytiotrophoblasts, cytotrophoblasts, villous fibroblasts, and Hofbauer cells; also intrapartum/postnatal routes[65,66]	Placental barrier breach via infected trophoblasts and fibroblasts, facilitating direct viral access to fetal circulation[69,70]	Infection/disruption of placental trophoblasts plus trafficking of infected maternal immune cells to decidua/placenta[82,84]
Placental vascular/immune consequence	Failed spiral artery remodelling from uNK dysfunction[52,53]; macrophage M1 repolarisation and Treg depletion[54-56,59]	Weak/delayed type I interferon response allows productive infection; subsequent pro-inflammatory response impairs trophoblast nutrient/oxygen exchange[68,71,73]	Impaired uNK angiogenic factor secretion (vascular endothelial growth factor, placental growth factor); simultaneous pro- and anti-inflammatory cytokine dysregulation[88,90,92 -
Key cytopathic/inflammatory feature	Chronic systemic cytokine storm (TNF-α, IL-6, IL-1β) flooding the decidua[15,24]	Direct neurotropic cytopathic effect: apoptosis of neural progenitor cells, radial glia[74-76]	Cellular enlargement, inclusion bodies, cell-cycle arrest in infected decidual/placental cells[85]
Primary neurodevelopmental outcomes	ADHD, mood/anxiety disorders, learning disability, subtle cognitive deficits—more pronounced in HEU children[108-111,124,125]	Microcephaly, cortical malformations, arthrogryposis, sensorineural hearing loss, intellectual disability (congenital Zika syndrome)[98,100,104]	Sensorineural hearing loss (progressive/delayed-onset), intellectual disability, cerebral palsy, motor/vision impairment[105-107,122,123]
Psychiatric associations	Secondary psychosis in advanced/poorly controlled disease[126,127]	ASD-associated features reported in early cohorts[112]	Increased ASD prevalence[115,116]; ADHD[117]; schizophrenia risk[131-133]
Epigenetic mechanism identified	Altered DNA methylation in immune/neurodevelopmental/stress-response genes in HEU children[134-136]	Emerging area of investigation, not yet well characterised[137]	DNA methylation, histone modification, microRNA changes in infected neural cells[138,94]

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; CMV: Cytomegalovirus; HEU: HIV-exposed uninfected; HIV: Human immunodeficiency virus; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; PlGF: Placental growth factor; TNF-α: Tumour necrosis factor alpha; Treg: Regulatory T cell; uNK: Uterine natural killer; VEGF: Vascular endothelial growth factor.

or immune architecture translating into a spectrum of neurological outcomes rather than a single uniform phenotype — reinforcing that the placenta, not the fetus directly, is often the proximate site of injury.

7.3. Research gaps and future directions

Despite substantial progress, critical knowledge gaps remain. First, the precise cell-specific mechanisms by which different pathogens interact with decidual and placental cell populations remain to be fully elucidated using advanced technologies, including single-cell and spatial transcriptomics, as well as organoid models that recapitulate the three-dimensional architecture of the maternal–fetal interface.[151] Understanding which decidual cell types are most vulnerable to each pathogen, how infected cells alter their secretory profiles, and how neighbouring cells respond to infection will enable the development of targeted interventions.

Second, the integration of inflammatory, metabolic, hormonal, and environmental signals by decidual immune cells and their collective roles in disease pathogenesis, including neurodevelopmental outcomes, preterm birth, fetal growth restriction, and pregnancy loss, requires comprehensive systems-level analysis. Notably, preterm birth itself, whether triggered by infection or non-infectious placental pathology such as placental accreta spectrum, which frequently necessitates emergency preterm delivery for maternal safety, independently contributes to adverse neurodevelopmental outcomes, underscoring preterm delivery as a convergent downstream pathway shared across both infectious and non-infectious placental disruption.[152] Multi-omics approaches integrating

genomics, transcriptomics, proteomics, metabolomics, and epigenomics from longitudinal pregnancy cohorts will be essential for identifying critical nodes in pathological pathways amenable to therapeutic intervention.[153]

Third, there is a pressing need to identify, validate, and clinically translate biomarkers that can reliably detect early immune dysregulation and stratify pregnancies at highest risk for adverse outcomes across diverse populations and settings. Current surveillance relies primarily on detecting infection itself, but biomarkers reflecting decidual dysfunction, placental insufficiency, or fetal brain injury would enable earlier identification of at-risk pregnancies and personalised intervention strategies. Promising candidates include specific cytokine profiles, cell-free fetal DNA, placental-derived exosomes, and neuroimaging findings, but rigorous validation in prospective studies is required. Longitudinal studies tracking children exposed to these infections in utero, especially those asymptomatic at birth, are essential to distinguish the specific contributions of viral infection, maternal inflammation, treatment exposures, and postnatal environmental factors to developmental trajectories. The HEU population, the Zika-exposed cohort without obvious microcephaly, and asymptomatic cCMV-infected children all require continued surveillance through adolescence and adulthood to fully characterise the spectrum and timing of neurodevelopmental and psychiatric manifestations.[26]

Finally, evaluating the efficacy and safety of interventions represents a critical translational priority. For HIV, determining optimal ART regimens that maximise viral suppression while minimising fetal neurodevelopmental toxicity, and testing adjunctive anti-inflammatory therapies to reduce residual MIA, could further improve outcomes for HIV-exposed children. For Zika virus, vaccine development for at-risk populations, evaluation of antiviral therapies if administered early in pregnancy, and assessment of neuroprotective strategies to mitigate fetal brain injury remain urgent priorities. For CMV, ongoing trials of antiviral therapy (valganciclovir) to prevent progression of neurodevelopmental impairment, maternal immunoglobulin to prevent fetal transmission, and vaccine development to prevent primary maternal infection during pregnancy could dramatically reduce the global burden of cCMV disease.

7.4. Clinical and public health implications

From a clinical perspective, this synthesis underscores the importance of integrated prenatal care that considers infectious disease screening, maternal immune status, and fetal neurodevelopmental surveillance as interconnected rather than isolated components. Obstetricians, infectious disease specialists, and developmental paediatricians must collaborate to optimise maternal health, prevent or treat infections, monitor fetal well-being, and ensure appropriate early intervention services for affected children.

From a public health perspective, these findings highlight the substantial and often underappreciated neurodevelopmental burden attributable to prenatal infections. Investment in prevention strategies, including vaccine development for Zika virus and CMV, vector control for Zika, universal HIV screening and treatment, and improved access to prenatal care, represents a critical opportunity to reduce the incidence of neurodevelopmental disabilities globally. Additionally, reducing health disparities in access to prenatal infection screening, treatment, and follow-up care is essential to ensure equitable outcomes for all children.

8. Conclusion

The decidua represents far more than a passive anatomical structure; it is an active, immunologically sophisticated interface that orchestrates the dialogue between mother and fetus throughout pregnancy. When viral infections disrupt this carefully choreographed system, the consequences extend from the cellular microenvironment through placental function to fetal brain development, ultimately manifesting as a spectrum of neurodevelopmental and psychiatric disorders that affect individuals throughout their lives. By elucidating pathogen-specific mechanisms of decidual dysregulation, identifying common pathways linking infection to neurodevelopmental outcomes, and developing targeted interventions informed by these mechanistic insights, we can work toward a future in which maternal infections no longer cast long shadows over the neurodevelopmental potential of the next generation.

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