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Congenital infectious encephalopathies from the intrapartum period to postnatal life

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A B S T R A C T

Congenital infections are a common but often underrecognized cause of fetal brain abnormalities, as well as fetal-neonatal morbidity and mortality, that should be considered by all healthcare professionals providing neurological care to fetuses and newborns.

Maternal infection with various pathogens (cytomegalovirus, Toxoplasmosis, Rubella virus, Parvovirus B19, lymphocytic choriomeningitis virus, syphilis, Zika virus, varicella zoster virus) during pregnancy can be transmitted to the developing fetus, which can cause multisystem dysfunction and destructive or malformative central nervous system lesions. These can be recognized on fetal and neonatal imaging, including ultrasound and MRI. Imaging and clinical features often overlap, but some distinguishing features can help identify specific pathogens and guide subsequent testing strategies. Some pathogens can be specifically treated, and others can be managed with targeted interventions or symptomatic therapy based on expected complications.

Neurological and neurodevelopmental complications related to congenital infections vary widely and are likely driven by a combination of pathophysiologic factors, alone or in combination. These include direct invasion of the fetal central nervous system by pathogens, inflammation of the maternal-placental-fetal triad in response to infection, and long-term effects of immunogenic and epigenetic changes in the fetus in response to maternal-fetal infection.

Congenital infections and their neurodevelopmental impacts should be seen as an issue of public health policy, given that infection and the associated complications disproportionately affect woman and children from low- and middle-income countries and those with lower socio-economic status in high-income countries. Congenital infections may be preventable and treatable, which can improve long-term neurodevelopmental outcomes in children.

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Key points

- Congenital infections should be considered as an important contribution to fetal central nervous system abnormalities, of both malformative and destructive nature.
- Specific imaging and clinical assessments can guide diagnosis, investigation, and treatment of congenital infection.
- Fetal infection and associated complications are driven by multiple pathophysiological mechanisms affecting the maternal-placental fetal triad.
- Congenital infections are a worldwide public health concern that represent social determinants of health that need to be prioritized for major changes in health care policy.

1. Introduction

Congenital infections are an underrecognized cause of structural and functional brain abnormalities that can result in a range of neurodevelopmental conditions expressed throughout childhood and adulthood. The developing fetal brain is vulnerable to the direct effects of an infectious exposure as well as indirectly by the effects of maternal inflammation through alteration of the intrauterine environment [1–3]. Congenital infections can be prevented by appropriate prenatal counseling and avoidance of exposures in certain situations [4–6]. Specific congenital infections, such as *Toxoplasma gondii*, are especially important to recognize early since prenatal treatment can reduce fetal transmission and improve outcomes [7,8]. Because of endogenous and exogenous stressors to the maternal-placental-fetal (MPF) triad, congenital infectious encephalopathies can contribute to malformative as well as destructive lesions of the brain. As these brain lesions are not

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always specific to congenital infections, accurate evaluations for maternal-fetal infections can help establish more precise diagnoses that would potentially avoid worsening complications. Counseling regarding identified or suspected infectious causes can be helpful for families regarding future pregnancies with risks for other family members.

The mnemonic "TORCH" – T" stood for *Toxoplasma gondii*, "O" for other agents, "R" for rubella, "C" for cytomegalovirus (CMV), and "H" for herpes simplex virus – is outdated yet continues to be used in clinical practice. The "other agents" of congenital infections has been significantly expanded over time to include Hepatitis B, human immunodeficiency virus (HIV), Parvovirus B19 (B19V), Lymphocytic choriomeningitis virus (LCMV), enterovirus, syphilis, borrelia burgdorferi, and Zika virus (ZIKV), among others. We therefore recommend that the term TORCH not be used, to be replaced by the specific congenital infections that need to be considered in relation to maternal reproductive health, pregnancy related risks, and geographic region of exposure. Negative serologic results or negative polymerase chain reaction (PCR) tests do not exclude congenital infections in all situations given limitations in sensitivity and specificity, as well as cross-reactivity (such as ZIKV with other flaviviruses).

When considering the potential for a congenital infection, prenatal medical history should include both preconception and pregnancy histories. Maternal environmental exposures, occupation, exposure to infants or young children, diet, source of water, pets, travel, symptoms of any illness, rural or urban living, and vaccination history are details to consider. First trimester pregnancy care (or when the pregnant patient first presents for prenatal care) typically screens for rubella, syphilis, and HIV, although additional serologies for toxoplasmosis and CMV are also performed in some centers and countries. Standards for trimester-specific maternal care requires uniformity of screening, challenged by healthcare disparities in low and middle-income countries and in medical deserts of high-income countries [9].

Congenital infectious encephalopathies are associated with a range of multi-system organ dysfunctions, neurosensory impairments, and neurodevelopmental disabilities (Table 1). Phenotypic variability in terms of organ involvement and injury severity is related to gestational timing and multiple gene-environment interactions affecting the health of the MPF triad. Genetic and epigenetic factors, gestational maturity at the time of exposure, and specific geographic region are examples of important variables to be considered [10,11]. The pattern of organ dysfunction helps guide prenatal and postnatal diagnostic evaluations. For example, an infant born with microcephaly and arthrogryposis with an epidemiological link to ZIKV should prompt evaluation for ZIKV infection in both the mother and infant. Alternatively, a small for gestational age newborn with a failed newborn hearing screen should prompt evaluation for CMV. Additional testing consisting of complete blood counts (CBC), liver function tests, cranial ultrasound (US), and brain magnetic resonance imaging (MRI) help guide decisions for postnatal treatments, for example antiviral therapy in congenital CMV.

Congenital infectious encephalopathies are associated with distinct abnormalities of the central nervous system which help guide targeted diagnostic laboratory testing (Table 2). For example, the pattern of calcifications, if present, can differ between pathogens: calcifications are usually periventricular with CMV, more scattered throughout the parenchyma with Toxoplasmosis, and subcortical in location with ZIKV. Calcifications are best recognized on cranial US and head computed tomography (CT); MRI sequences have added sensitivity regarding specific malformative or destructive lesions, with variable sensitivity to hemorrhage and calcifications depending on sequence modalities. The absence of calcifications does not exclude infectious etiologies.

The following clinical histories demonstrate a range of clinical presentations, highlighting pathogen-specific approaches to prenatal and postnatal care.

2. Case 1

A 25-year-old woman, gravida 2 para 1, at six weeks into her pregnancy had a low-grade fever, fatigue, nausea, and headache lasting two weeks. Her husband had similar symptoms. They had a healthy 3-year-old daughter. No recent travel, animal exposures, or gardening activities were reported. They live in a suburban community in a single-family home. She was negative for SARS-CoV-2 via PCR test. The obstetrician pursued an infectious workup which included positivity for Lyme, Varicella IgM (previously vaccinated), EBV IgM, and CMV IgM, with low IgG avidity. Prenatal US at 14 weeks documented a fetal head circumference at the 29th percentile, as well as a small echogenic focus in the bowel. By 18 weeks of gestation, US showed a head circumference at less than the 1st percentile, a thickened placenta, and ascites. CMV PCR was positive in amniotic fluid. Fetal MRI at 20 weeks of gestation showed diffuse cortical injury with restricted diffusion, shortened corpus callosum, massive fetal ascites, hepatomegaly, and a thick placenta (Fig. 1). The fetus was diagnosed as having severe congenital CMV infection due to maternal primary CMV infection. The pregnancy was terminated given the likely very poor prognosis. Placental pathology was consistent with extensive CMV villitis. Autopsy of the fetal brain was consistent with CMV meningoencephalitis, and CMV immunohistochemical stain confirmed the presence of a generalized CMV infection.

3. Case 2

The neurology team was consulted in the neonatal intensive care unit (NICU) for a 6-day-old male, born at 36 weeks of gestation, in the context of prenatal diagnosis of ventriculomegaly and corpus callosum dysgenesis. His mother was primigravida with an uncomplicated pregnancy without infectious symptoms. An obstetrical US at 21 weeks of gestation documented bilateral mild ventriculomegaly and an absent corpus callosum, confirmed on fetal MRI. Delivery was performed at 36 weeks via cesarean section following documentation of a non-reassuring fetal heart tracing. The infant was transferred to our NICU on CPAP due to respiratory distress and apneas, although he initially showed a

Table 1
Multisystem sequalae of congenital infectious encephalopathies.

Sequelae	Toxo	Rub.	CMV	HSV	B19V	Syph	VZV	HIV	LCMV	ZIKV
Intellectual disability	X	X	X	X		X	X	X	X	X
Seizures	X	X	X	X		X	X	X	X	X
Blindness	X	X	X	X		X	X	X	X	X
Hearing loss	X	X	X			X		X		X
Motor disability	X	X	X	X	X	X	X	X	X	X
Learning disability	X	X	X	X	X	X	X	X	X	X
Limb deformity						X	X			X
Cardiac dysfunction		X			X					
Hepatic dysfunction					X					
Endocrine dysfunction	X	X								

B19V: Parvovirus B19 virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; LCMV: lymphocytic choriomeningitis virus; Rub.: Rubella virus; Syph: syphilis; Toxo: Toxoplasmosis; VZV: varicella zoster virus; ZIKV: Zika virus.

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Table 2
Common fetal brain MRI findings in congenital infectious encephalopathies.

Fetal CNS Imaging Findings	CMV	Toxo.	LCMV	B19V	ZIKV	Syph.	Rub.	VZV
Microcephaly	**X**	X	X		X Severe	X	**X**	**X**
Macrocephaly		X	X					
Ventriculomegaly	**X**	X	X	X	X	X		**X**
Hydrocephalus		X	X					
Cystic abnormalities	**X**				X			
Calcifications	**X** **PV**	X Diffuse BG	X PV	X (Rare)	X SC BG	X		
White matter abnormalities	**X**				**X**			
Corpus callosum dysgenesis	X		X		X			
Cortical malformations	X	X	X	X (Rare)	X			
Cerebellar hypoplasia	X		X	X	X			
Ischemic lesions/Porencephaly	X	X	X	X		X		X
Intracranial hemorrhage	X		X	X		X		
Parenchymal atrophy	**X**				X			
Microphthalmia		X			X		X	X
Arthrogryposis					X			

B19V: Parvovirus B19 virus; BG: basal ganglia; CMV: cytomegalovirus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; LCMV: lymphocytic choriomeningitis virus; PV: periventricular; Rub.: Rubella virus; SC: subcortical; Syph: syphilis; Toxo: Toxoplasmosis; VZV: varicella zoster virus; ZIKV: Zika virus.

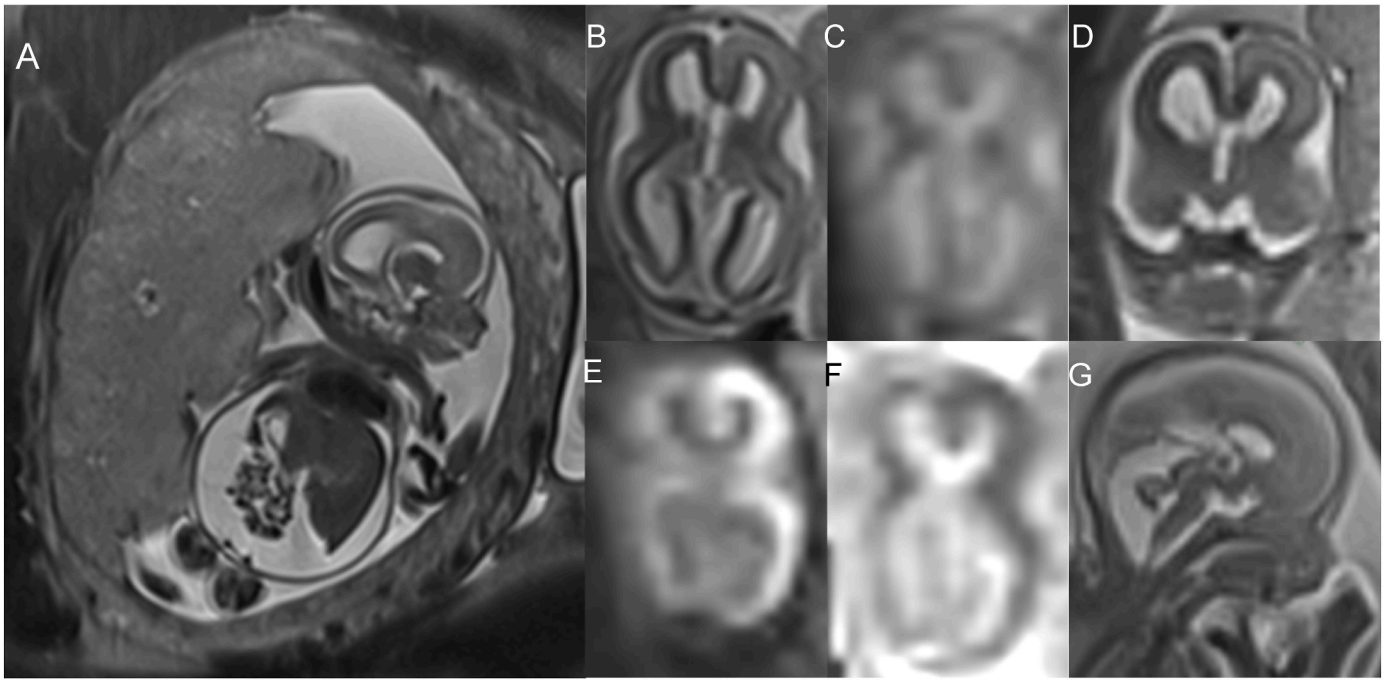

Fig. 1. (Case 1) Fetal MRI at 20 + 2 weeks of fetus diagnosed with congenital CMV (A: coronal body showing placentomegaly, fetal ascites and hepatomegaly; B: axial T2 showing cerebral ventriculomegaly, parenchymal thinning, and abnormal signal throughout the left cerebral hemisphere; C: axial EPI showing abnormal signal in the right hemisphere; D: coronal T2 showing ventriculomegaly and abnormal signal in left hemisphere; E–F: axial DWI (E) and ADC (F) showing restricted diffusion throughout left hemisphere and parts of right hemisphere; G: sagittal T2 showing short corpus callosum and small posterior fossa structures).

favorable transition with Apgar scores of 6 and 9 at 1 min and 5 min respectively. Anthropometric measurements on admission were a weight of 1.8 kg (below first percentile), a length of 40 cm (below first percentile), and a head circumference of 28 cm (below first percentile); he was thus considered to be small for gestational age (SGA). Initial bloodwork was significant for thrombocytopenia. An electroencephalogram was negative for seizures but documented mild excessive discontinuity for age. Head US showed moderate to severe ventriculomegaly, corpus callosum dysgenesis, and periventricular and basal ganglia calcifications (Fig. 2). Brain MRI showed microcephaly, abnormal cortex (dysgyria and polymicrogyria), periventricular calcifications, and caudothalamic cysts (Fig. 3). Ophthalmology evaluation revealed macular chorioretinal lacunae and possible optic nerve hypoplasia. A positive urine CMV PCR was reported at 2 weeks of age, confirming congenital CMV infection. Valganciclovir therapy was initiated. Placental pathology was not obtained. He was discharged home at 1 month of chronological age with oxygen supplementation and a gastrostomy tube for feeding. At 3 months of age, he had early markers of developmental delay and limb hypertonia on neurological examination and normal hearing sensitivity by formal audiology testing.

4. Case 3

A 6-month-old girl was seen in neurology clinic for probable congenital CMV following an unremarkable pregnancy and delivery at term to a mother who was gravida 2, para 1 and reported no infectious

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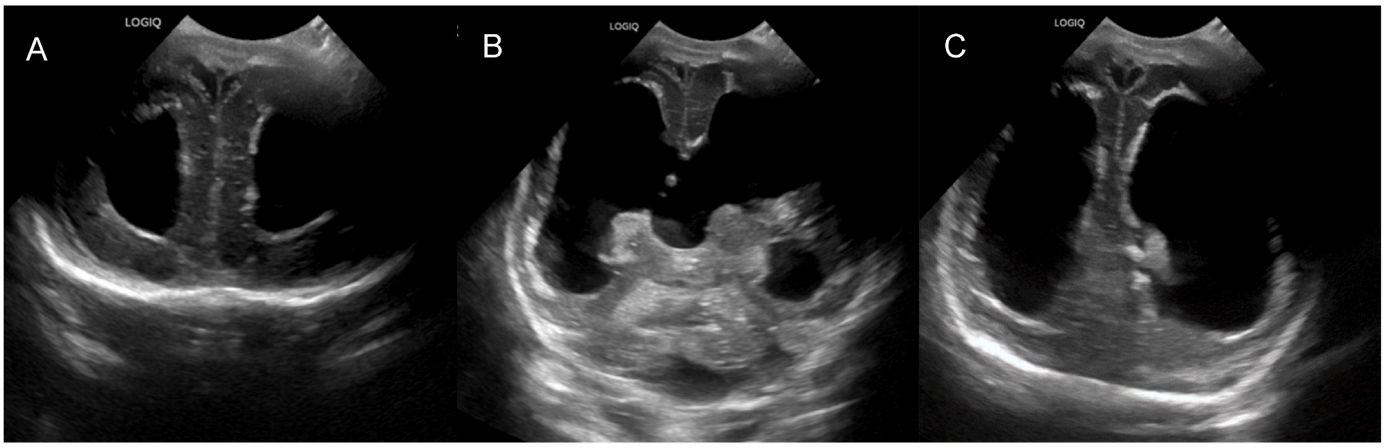

Fig. 2. (Case 2) Neonatal HUS at 5 days of age (36 + 5 corrected GA) of infant diagnosed with congenital CMV (A–C: coronal views showing ventriculomegaly and periventricular calcifications).

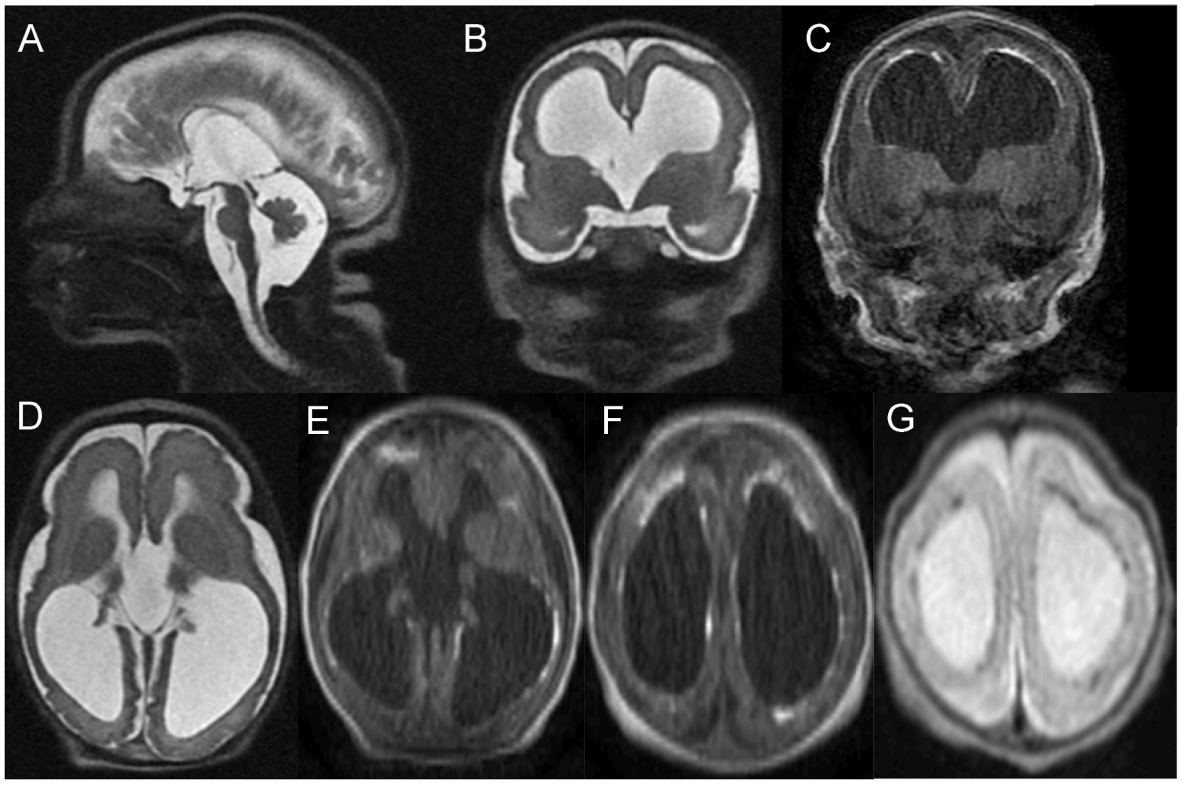

Fig. 3. (Case 2) Neonatal brain MRI at 6 days of age of infant diagnosed with congenital CMV (A: sagittal T2 sequence showing microcephaly, thinning of corpus callosum and small posterior fossa structures; B–C: coronal T2 (B) and T1 (C) sequences showing abnormal cortical gyration, enlarged opercula, perisylvian polymicrogyria, ventriculomegaly, and white matter volume loss; D–E: axial T2 (D) and T1 (E) sequences showing similar findings to D and E; F–G: axial T1 (F) and modified T2 (G) sequences showing ventriculomegaly and periventricular calcifications).

symptoms. Routine fetal USs were reportedly normal. Her older toddler was at home for most of her pregnancy, although was in daycare for a few weeks early in the first trimester. She denied travel during the pregnancy and the family lived in an urban community with a cat. Prior to discharge from the birth hospital, the infant failed the hearing screen on the right with subsequent audiology testing confirming severe right sensorineural hearing loss and normal left-sided function. She was seen in otolaryngology and urine CMV PCR was sent (1 month of age), which was positive. Brain MRI (3 T) documented normal structures. Ophthalmology assessment was normal. Bloodwork documented transaminitis and positive CMV serum PCR. Retrospective analysis of the neonatal bloodspot was negative for CMV. She was seen at 6 weeks of age by infectious disease with a normal examination. Following discussion with the family, the decision was to start Valganciclovir therapy to help protect hearing deficits to the left ear and neurodevelopment based on presumed congenital CMV infection. She had a normal early neurodevelopmental profile on neurological assessment.

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5. Congenital infections to be considered by the fetal-neonatal neurologist

5.1. Cytomegalovirus (CMV)

5.1.1. Epidemiology

CMV, part of the *Herpesviridae* family, is a ubiquitous virus that affects most of the general population and is the most common malformation-causing congenital infection worldwide. From 40 to 90 % of adult women are exposed to CMV in their lifetime, a number that varies depending on geographic location and socio-economic background [12,13]. Primary infection is often asymptomatic or mildly symptomatic in immunocompetent individuals. Maternal-fetal transmission can occur with both primary and non-primary infection – which may represent reactivation of latent virus or re-infection by a different viral strain [14]. About 30 % of gestational parents infected with CMV for the first-time during pregnancy will transmit the virus to their fetus, with about 13 % of these infants presenting with symptomatic congenital CMV at birth. In seropositive gestational parents that are infected (non-primary infection), less than 2 % will pass on the virus to their fetus, although this may be underestimated based on available studies. Congenital CMV should thus not be fully excluded as a possibility in a pregnant patient with "protective" serologies on early testing.

5.1.2. Clinical and imaging findings

Fetal and neonatal imaging findings are summarized in Table 3 [15–17]. Placental abnormalities may be noted on US. Maternal pre-eclampsia, preterm birth, and intrauterine fetal demise (IUFD) are possible.

5.1.3. Investigations and treatment

Evidence of maternal infection can be ascertained using CMV-specific IgM and IgG antibodies. Positive IgM antibody and negative IgG (IgM+/IgG−) is consistent with recent primary CMV infection, although this is a transient marker. Often, by the time CMV serologies are tested, there has been IgG seroconversion, at which point CMV-specific IgG avidity is required; low IgG avidity is consistent with a recent primary infection [18]. CMV-specific IgM antibodies in isolation should be interpreted with caution since a positive result may represent primary or secondary infections and a negative result may represent an infection earlier in the pregnancy with subsequent normalization of the IgM levels by the time the suspicion of congenital CMV arises. Fetal infection can be ascertained non-invasively by imaging when typical features are present; invasive confirmatory testing via amniocentesis is possible by using CMV-PCR or CMV culture on amniotic fluid. Postnatal confirmation of congenital CMV infection is done via CMV-PCR in saliva, serum, blood spots, and urine, although urine PCR appears to be the most sensitive and specific. Testing must ideally be within 3 weeks of age to confirm congenital CMV [19,20]. Postnatal therapy with Valganciclovir is indicated in cases of symptomatic congenital CMV, especially when there is involvement of the CNS [19,21]. Prenatal therapy is not available currently, although trials are ongoing for maternal treatment with Valaciclovir [22,23]. Simple hygienic precautions are recommended to reduce exposure to CMV in the community, especially for pregnant patients in contact with children and those without pre-conceptual immunity [24]. Vaccination to CMV has been actively investigated for a few decades, although controversy exists around safety and efficacy [25].

5.2. Toxoplasmosis

5.2.1. Epidemiology

Toxoplasma gondii is an intracellular parasite that is a common cause of congenital infection, with an estimated incidence of 1/3000 to 1/10,000 live births, usually depending on geographic and socioeconomic factors. Felines are a primary reservoir, and exposure to oocysts excreted

Table 3
Summary of clinical features of congenital infectious encephalopathies in the fetus and newborn.

Pathogen	CMV	LCMV	ZIKV	VZV	B19V	Rubella	Toxoplasmosis (*Toxoplasma gondii*)	Syphilis (*Treponema pallidum*)
Family/Category	*Herpesviridae*	*Arenaviridae*	*Flaviviridae*	*Herpesviridae*	*Parvoviridae*	*Matonaviridae*	Intracellular parasite	Spirochete bacteria
Transmission	Bodily fluids	Rodents	Mosquito Sexual	Droplets Aerosols	Droplets Secretions	Droplets	Cat feces Soil Food/Meat	Sexual Blood
Clinical features in the fetus and newborn	IUGR CR HSM SNHL	IUGR Hydrops Ascites Cardiomegaly HSM CR	IUGR Arthrogryposis Hypertonia Seizures ON atrophy CR Microphthalmia SNHL	IUGR Limb hypoplasia Microphthalmia Cataracts Nystagmus ON atrophy CR Horner syndrome Rash Seizures	Hydrops Ascites Pericardial effusion Enlarged placenta Echogenic bowel	CHD Glaucoma Cataracts CR HSM Purpuric rash Microcephaly Encephalitis SNHL	IUGR Microcephaly Hydrops Ascites Pericardial effusion HSM CR Microphthalmia ON atrophy SNHL Seizures Rash	Stillbirth IUGR HSM Hydrops Ascites Pericardial effusion Rash Rhinitis Osteochondritis CR SNHL
Neuroimaging features in the fetus and newborn	Microcephaly PMG Schizencephaly Calcifications (PV) Cysts (PV) VM CH	Microcephaly VM Calcifications (PV) CC dysgenesis ICH CH Cortical malformations	Microcephaly (severe) VM CC dysgenesis Calcifications (SC, BG) BS hypoplasia CH Cortical malformations	Microcephaly VM Porencephaly	ICH VM CH Calcifications (cortex, BG) Cortical malformations	Microcephaly ICH	VM Hydrocephalus Calcifications (diffuse) Cortical malformations	ICH IVH VM Edema

Legend: BS: brainstem; BG: basal ganglia; CC: corpus callosum; CH: cerebellar hypoplasia; CHD: congenital heart defect; CR: chorioretinitis; HSM: hepatosplenomegaly; ICH: intracranial hemorrhage; IUGR: intrauterine growth restriction; IVH: intraventricular hemorrhage; SNHL: sensorineural hearing loss; ON: optic nerve atrophy; PMG: polymicrogyria; PV: periventricular; SC: subcortical; TMP-SMX: trimethoprim-sulfamethoxazole; VM: ventriculomegaly.

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in feces as well as through viable cysts in undercooked meat from infected animals are the common means of infection [26]. Congenital toxoplasmosis usually occurs after transmission of the parasite from a previously seronegative gestational parent (primary infection) to the fetus after exposure during pregnancy or shortly prior to conception, although reactivation of toxoplasmosis in an immunocompromised pregnant person or reinfection with a more virulent strain of toxoplasmosis are also possible [7,27]. Rates of transmission vary depending on gestational age. The variability in severity may be partially explained by the virulence of different strains of *T. gondii*.

5.2.2. Clinical and imaging findings

Typical fetal and neonatal imaging findings in congenital toxoplasmosis are summarized in Table 3 [7,27]. Fetal demise is a concern. Additional neonatal clinical features include thrombocytopenia, disseminated intravascular coagulation, hepatitis, myocarditis, pneumonitis, hepatosplenomegaly, sepsis-like illness, and rash (described as petechial or "blueberry muffin"-like) [28].

5.2.3. Investigations and treatment

Diagnosis of congenital toxoplasmosis combines the typical neuroimaging or clinical features with serological tests and PCR assays. Recent maternal infection is suspected with a positive anti-*Toxoplasmosis* IgM, with negative or positive IgG, although this must be interpreted with caution. Indeed, a positive IgM may represent a false positive or evidence of a chronic infection; a negative IgM in the presence of positive IgG may represent normalization of the IgM titers between the initial infection and the moment when the serologies were drawn [7,27]. Confirmation in a reference laboratory using more advanced serological testing is usually necessary. Evidence of fetal infection (in the context of maternal infection) can be shown non-invasively by imaging findings consistent with congenital toxoplasmosis or invasively with positive *Toxoplasma* PCR in amniotic fluid. Postnatal confirmation of congenital toxoplasmosis in the neonate consists of a positive *Toxoplasma* IgG with either positive *Toxoplasma* IgM or IgA, although the infant can still be considered symptomatic or asymptomatic depending on the presence of clinical or paraclinical involvement related to toxoplasmosis [7]. *Toxoplasma* PCR in the blood, cerebrospinal fluid (CSF), or urine of the neonate appears to have a variable but low sensitivity, although CSF PCR may be a useful adjunct in patients with radiological features concerning for toxoplasmosis but equivocal serologies. The prenatal treatment regimen depends on gestational age and includes spiramycin, pyrimethamine, sulfadiazine and leucovorin [7,27,29]. Postnatal therapy consists of a combination of pyrimethamine, sulfadiazine, leucovorin, and possibly prednisone for severe chorioretinitis; specific regimens and dosing are described elsewhere [7]. Simple preventive measures during pregnancy, including cooking meat appropriately, avoiding raw seafood, and limiting contact with cat feces and soil, are recommended [24,27].

5.3. Lymphocytic choriomeningitis virus (LCMV)

5.3.1. Epidemiology

LCMV is an RNA virus in the Arenaviridae family that causes congenital infection and CNS abnormalities [28,30]. Rodents, including house mice, are an environmental reservoir, and they can develop a chronic asymptomatic infection whereby they shed virus throughout their lifespan in bodily fluids and feces. Humans can encounter LCMV through aerosolized virus, fomites, contaminated food, or rodent bites. Although worldwide distribution is not well known, studies have reported a populational seroprevalence of LCMV antibodies ranging from 3.3% to 6.8%, increasing in professionals exposed to rodents [31–35]. Most primary infections are asymptomatic or consist of a non-specific viral illness, although some adults can present with CNS infection. The incidence of LCMV infection in pregnant people is not well known, however maternal-fetal transmission is recognized. Congenital LCMV is likely underrecognized as it is not typically part of the usual workup for suspected congenital infections and obtaining serum serologies may be limited in some centers or commercial laboratories.

5.3.2. Clinical and imaging findings

Findings reported on fetal and neonatal imaging are summarized in Table 3 [28,30,36]. Other postnatal clinical findings include chorioretinitis, skin abnormalities, anemia, and thrombocytopenia.

5.3.3. Investigations and treatment

Prenatal diagnosis can be made non-invasively with fetal imaging findings and maternal serologies; a positive IgM with negative IgG is consistent with a recent infection, although there may be IgG seroconversion and even IgM normalization by the time the suspicion for LCMV arises in pregnancy, complicating the interpretation (LCMV IgG avidity has not been developed at this time) [28,30]. The other testing option is via amniocentesis with direct viral PCR on amniotic fluid. Postnatal diagnosis can be made with serum serologies in the neonate (positive IgM and IgG would be consistent with congenital infection). Preventive measures for pregnant people are aimed at limiting contact with rodents and avoiding cohabitation with house mice [37].

5.4. Parvovirus B19 virus

5.4.1. Epidemiology

Parvovirus B19 (B19V) is a DNA virus, part of the *Parvoviridae* family that is common in the community setting and well known to cause a specific phenotype of congenital infection [38–41]. The virus has a particular tropism for the placenta and erythroid precursor cells. Epidemiological studies report a seroprevalence of around 15 % in children, 50 % in young adults, and 85 % in elderly individuals. When infected, 25 %–50 % of people are asymptomatic; symptomatic individuals can have a non-specific viral syndrome or the more classic erythema infectiosum. Prior exposure to B19V with IgG seroconversion likely confers appropriate immunity to the mother and precludes reinfection and fetal transmission. When a pregnant person is infected, maternal-fetal transmission is possible, the risk of which is between 17 % and 35 % [38].

5.4.2. Clinical and imaging findings

The phenotype of fetal infection is driven by the involvement of hematopoietic cells, although infection can also involve other cell types such as the cardiomyocytes. Evidence for infection on imaging is summarized in Table 3. Intrauterine fetal demise can occur in severe cases. Neurological involvement is rare and likely results from a combination of the infection itself and the severe fetal anemia and thrombocytopenia. Potential fetal and neonatal brain imaging findings are also summarized in Table 3 [42–46].

5.4.3. Investigations and treatment

Fetal infection can be investigated by combining the clinical phenotype and maternal serologies and proven invasively via amniocentesis with B19V PCR. A negative IgM should be interpreted with caution when congenital Parvovirus B19 is suspected; indeed, both IgM and IgG can be negative if tested within a week of the primary infection, and IgM could have normalized by the time the clinical suspicion of congenital Parvovirus B19 arises [38]. The sensitivity of IgM detection has been reported to be up to 70 % 8–12 weeks after the primary infection. The viral infection itself does not have a specific treatment, however, the hydropic and anemic fetus can be treated with intrauterine transfusions [38]. Basic hygiene measures, including hand washing, especially when in contact with younger children, should be done as preventive measures during pregnancy [24].

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5.5. Zika virus (ZIKV)

5.5.1. Epidemiology

ZIKV is a member of the *Flaviviridae* family that rose to popular knowledge in 2015 after a large outbreak in Brazil and a newly recognized severe congenital syndrome led to the declaration of a public health emergency of international concern in early 2016. Although comprehensive surveillance is not widespread, the virus has established a variable presence in countries in South and Central America, the Caribbean, South-East Asia, and Sub-Saharan Africa, as well as Mexico and some US territories, although cases and outbreaks have decreased drastically in all regions since the 2015–2017 epidemic [47,48]. ZIKV is a mosquito-borne virus and may also be sexually transmitted from an infected partner. It usually causes a mild febrile illness with arthralgia, conjunctival erythema, and rash, or may be asymptomatic. In a pregnant person, maternal-fetal transmission is a major concern with an increased risk for fetal microcephaly and other ZIKV-related birth defects from infection early in pregnancy [47,49–51].

5.5.2. Clinical and imaging findings

Congenital Zika syndrome (CZS) is the severe neurological phenotype that includes significant injury to the developing brain seen as severe micrencephaly and other findings summarized in Table 3 [52–56]. Compared to CMV and Toxoplasmosis, the calcifications in CZS are typically subcortical in a bandlike distribution and may also be present in the basal ganglia. Infants with CZS can also have postnatal onset of microcephaly that is not apparent at birth [57]. Ophthalmological examination can show microphthalmia, colobomas, chorioretinal atrophy, pigmentary retinal mottling, and optic nerve hypoplasia [58,59].

5.5.3. Investigations and treatments

If plausible from an epidemiological standpoint, maternal infection can be investigated with ZIKV PCR in serum or urine (during the acute infection) or specific *anti*-ZIKV antibodies: a positive IgM would suggest a recent infection in the appropriate clinical context [49]. IgM levels normalize after about 12 weeks from infection and *anti*-ZIKV IgG titers are not well validated. Cross reactivity with other flaviviruses is possible and could cause a false positive result, especially in places with circulating Dengue virus; plaque reduction neutralization test (PRNT) is helpful in this context [60]. ZIKV PCR in the fetus (done invasively via amniocentesis) or in the neonate shortly after birth can serve as confirmatory testing. There is no specific anti-viral therapy and treatments are aimed at supportive care. Preventive measures in pregnancy include avoiding travel to regions of the world with ZIKV outbreaks and taking precautions to avoid mosquito bites [47]. Preventive measures apply to the pregnant person's partner as well [61].

5.6. Syphilis

5.6.1. Epidemiology

Syphilis is an acquired disease caused by the spirochete bacterium *Treponema pallidum*, usually transmitted via sexual contact. Maternal-fetal transmission is possible at any time in an affected and untreated mother, causing congenital syphilis, which has seen a relative resurgence in recent years with increasing rates of syphilis in women of childbearing age [9,62,63]. Transmission of *Treponema pallidum* to the fetus is higher in the primary and secondary stages of syphilis compared to latent stages, although is possible in all stages.

5.6.2. Clinical and imaging findings

Prenatal and neonatal clinical signs of congenital syphilis are summarized in Table 3. Neurological abnormalities are less typical, but have been described [64,65]. Premature labor and intrauterine fetal demise are possible.

5.6.3. Investigations and treatment

Diagnosis of maternal infection is done using serologies (treponemal and non-treponemal, details of which are outside the scope of this article), positive PCR on a typical skin lesion or bodily fluid, or direct identification of spirochetes on microscopy. Diagnosis of fetal infection can be inferred non-invasively by combining typical clinical signs and evidence of maternal infection. Invasive diagnosis can be done via amniocentesis using PCR and microscopic evaluation; however, these are not widely available. Neonatal diagnosis can be confirmed with treponemal and non-treponemal serologies, PCR and microscopy [62–65]. Treatment of congenital syphilis involves maternal treatment with Benzathine penicillin G to minimize the risk of adverse pregnancy outcomes. Severe anemia and hydrops can potentially be treated with intrauterine transfusions, although this therapy has not been well studied in congenital syphilis. Treatment of the neonate after delivery involves a form of penicillin G and varies depending on adequacy of maternal treatment, clinical examination of the newborn, and serological testing [65]. Treatment of positive mothers and their partners with penicillin and minimizing high-risk sexual behaviors are essential parts of the prevention of congenital syphilis [9].

5.7. Rubella

5.7.1. Epidemiology

Rubella virus is an RNA virus in the Matonaviridae family with a single stable serotype [66,67]. Rubella infection was one of the first prototypical diseases known to affect the fetal brain. Transmitted through droplets and direct contact, infection in children and adults is usually asymptomatic or mildly symptomatic, with non-specific fever, rash, and lymphadenopathy. Prior infection or complete vaccination confers immunity. The virus can be transmitted from the infected gestational parents to the fetus and cause congenital rubella syndrome (CRS), especially if contracted in the first 16 weeks of pregnancy. Widespread vaccination efforts since the 1960s have drastically reduced the burden of this disease; however, CRS remains a major cause of congenital malformation worldwide, especially in populations with lower vaccination rates.

5.7.2. Clinical and imaging findings

The classic triad of CRS consists of cataracts, congenital heart defects, and sensorineural hearing loss, although other signs can be seen, as summarized in Table 3 [66,67].

5.7.3. Investigations and treatment

Maternal infection can be diagnosed using serologies, although the anti-Rubella IgM decreases rapidly to become undetectable around 8 weeks after primary infection, which may complicate diagnosis if concern for CRS arises later. Avidity assays of the anti-Rubella IgG can be helpful in documenting a recent infection (with low IgG avidity) in the appropriate clinical context if IgM is negative. Diagnosis of fetal infection can be done invasively via amniocentesis with PCR of amniotic fluid or fetal cord blood. Neonatal diagnosis of infection can be done using serologies (positive IgM) or PCR in bodily fluids (nasal swab, saliva, serum, urine, or CSF) [66,67]. In the absence of antiviral therapy to Rubella, treatment is mostly supportive and tailored to the specific clinical and paraclinical signs in the neonatal period, including anti-seizure medications. Prevention of CRS is obtained through population vaccination efforts for children and unvaccinated people of childbearing age, with which eradication of the disease is possible.

5.8. Varicella-zoster virus (VZV)

5.8.1. Epidemiology

VZV is a DNA virus part of the *Herpesviridae* family. It is well known to cause varicella (chickenpox) as a primary infection, characterised by fever, malaise, and a typical generalized vesicular rash. VZV then

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remains dormant in sensory nerve ganglia and can subsequently reactivate as herpes zoster (shingles). Maternal-fetal transmission can occur with primary infection in pregnancy, causing congenital varicella syndrome (CVS) [68–70]. There are reports of CVS in the context of herpes zoster (reactivation), possibly with disseminated herpes zoster, although the risk and incidence of this is not well known.

5.8.2. Clinical and imaging findings

Fetal and neonatal signs of CVS are summarized in Table 3 [68,70].

5.8.3. Investigations and treatment

Maternal infection can be assessed using serologies (IgM and IgG) and PCR of vesicle swabs. Fetal infection is confirmed invasively via amniocentesis with PCR of amniotic fluid or fetal blood. Neonatal investigations in the appropriate clinical context include VZV-specific IgM and PCR of serum or swabs from vesicular lesions [68,70]. Pregnant women with chickenpox can be treated with acyclovir, although the benefit in terms of reduction of CVS is unclear. Neonates with severe disseminated VZV infection should receive antiviral therapy with acyclovir and supportive measures tailored to their clinical signs, including antiseizure medications. Select neonates may benefit from receiving VZV immunoglobulins (VZIG) as postexposure prophylaxis, although this is only if the mother had signs or symptoms consistent with varicella around the time of delivery (5 days prior to 2 days after delivery). Prevention of CVS is mostly through vaccination of children and non-immune women of childbearing age [24].

6. Maternal-placental-fetal (MPF) triad and pathophysiology of congenital infection

Although pathogens have differing disease pathways, a common diagnostic approach can be applied that more effectively anticipates the impact of congenital infections on the complex interactions between the mother, the placenta, and the fetus (i.e. the MPF triad): 1) active maternal infections may induce an exaggerated immune activation within the MPF triad with organ-specific inflammatory effects throughout pregnancy; 2) transplacental pathogen transmission and infection of the fetal CNS and other organs may result in direct injury to the fetus; and 3) long-term effects across the lifespan may result from adverse effects by congenital infections affecting the fetal exposome.

6.1. The normal MPF triad

The placenta is the main point of contact between the maternal and fetal systems, with juxtaposition of the placental extravillous trophoblasts to the uterine decidua basalis. Adaptive maternal immune responses occur at the placental junction to maintain positive interactions between the complex immunogenic systems within the MPF triad. These adaptations consist of a pro-inflammatory state that predominates during the implantation phase, an anti-inflammatory state that exists during the fetal growth phase of the second and early third trimesters, and a pro-inflammatory state that resumes in the late third trimester in preparation for a healthy labor and delivery [71–74]. Maternal immune cells, including macrophages and lymphocytes (natural killer cells, T cells, B cells), maintain the placental microenvironment by promoting adaptive angiogenesis and trophoblast invasion, while regulating immune activation through anti-inflammatory cell linages, cytokines, and chemokines [75].

6.2. Disruption of the brain-placental axis

Maternal immune regulation of the placental microenvironment may be disturbed by congenital infections resulting in a combination of factors that have downstream effects on the developing fetus [1–3,74,76].

Infection in the mother induces an elevated inflammatory state, termed maternal immune activation (MIA), which involves an increase in circulation of various inflammatory markers and pro-inflammatory molecules [74,76,77]. MIA, even in the absence of direct fetal infection, has been shown to produce negative pregnancy outcomes, such as fetal demise and preterm delivery, as well as short-term effects on the neonate, including an increased risk of perinatal brain injury and abnormal lung development [74,76]. MIA has been linked in epidemiological studies to neurodevelopmental and psychiatric disorders, such autism spectrum disorder, attention deficit-hyperactivity disorder, depression, and schizophrenia [77–82]. Animal model studies of MIA have demonstrated that immune activation in a pregnant non-human primate or rodent is associated with pathological effects in offspring, including decreased brain volumes, differences in behavioral testing, changes in cortical architecture, and modifications in the expression of genes regulating central nervous system development [77,79,83,84]. Human studies have shown that increased maternal serum markers of MIA correlate with some neonatal brain connectivity measures, amygdala volumes, and performance on standardized developmental testing [78,85]. Although further studies are needed to confirm the pathological process, abnormal fetal brain development in the context of MIA may in part be driven by altered microglial development and signaling [82].

Following maternal infection, placental invasion is well recognized in both viral and non-viral infections [72,86]. *Toxoplasmosia gondii* invades placental cells via trophoblast surface receptors and pathological studies have demonstrated lymphohistiocytic chronic villitis, diffuse inflammation, and granulomas [86]. Placental changes from CMV infection include acute and chronic intervillositis, cytomegalic inclusions, vascular sclerosis, calcifications, and chronic lymphoplasmacytic villitis [72,86]. Similarly, placental infection with ZIKV may cause various findings including villous edema, increased fibrin deposits, deciduitis, and chronic villitis [86].

Pathological changes in the placenta from infection are represented by the ischemic placental syndrome (IPS). Ischemia within the uteroplacental microenvironment induces oxidative stress and results in the release of inflammatory molecules. These disease pathways worsen endothelial damage and may also contribute to adverse pregnancy outcomes, such as hypertension, preeclampsia, HELLP syndrome, and eclampsia. Adverse fetal outcomes may include fetal growth restriction, prematurity, and fetal demise [87,88]. Animal models and human studies have shown that IPS can occur through direct infection, or indirectly through maternal inflammatory responses, in both cases resulting in placental insufficiency and maternal preeclampsia [87].

Congenital infections cause an elevated fetal inflammatory state in the fetus with elevated cortisol and pro-inflammatory molecules which may harm fetal growth and development [74,76,89]. The term fetal inflammatory response (FIR) has been applied to describe the systemic inflammation in the fetus, usually in terms of increased inflammatory markers and cytokines, such as IL-6, in response to inflammation of the uteroplacental environment [90,91]. FIR has mostly been described in the context of chorioamnionitis and funisitis but may also include uteroplacental infections that are associated with congenital infections. FIR has been associated with multiple consequences on pregnancy and fetal-neonatal outcomes [90–92]. Transcriptome analysis in neonates born with FIR have shown increased concentrations of pro-inflammatory molecules and upregulation of various genes associated with an inflammatory profile [90].

As a more recent example of the impact of congenital infection on the MPF triad, infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and ZIKV appears to impact the developing fetus even in the absence of clear destructive or malformative brain changes. Recent studies in the context of the SARS-CoV-2/COVID-19 pandemic have reported signs of acute and chronic inflammation in the placentas of pregnant mothers infected with SARS-CoV-2, including chronic histiocytic intervillositis, increased fibrin deposition, and villous trophoblast necrosis [93–96]. SARS-CoV-2 infection in a pregnant individual – like other viral infections such as Severe Acute Respiratory Syndrome

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Coronavirus 1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV) and Influenza – may be associated with poor pregnancy and fetal outcomes, including preeclampsia, preterm birth, fetal growth restriction, miscarriage, and stillbirth [94]. Although there have been no reports of major congenital malformations in fetuses exposed to SARS-CoV-2 during pregnancy, some studies have noted an increased rate of neurodevelopmental issues in these infants [97–99]. Similarly, exposure to ZIKV during pregnancy appears to induce a systemic inflammatory response in infants with CZS and their mothers [89]. Even in the absence of CNS injury, infants exposed to ZIKV in utero seem to be at a higher risk of neurodevelopmental issues at 18 months [100], which may suggest an additional and independent contribution of an inflammatory response during pregnancy on the developing brain. Thus, abnormal immune activation of the MPF triad (MIA, IPS and FIR) with congenital infection either independently or in combination may correlate with adverse early and late outcomes.

6.3. Pathogen-related direct brain fetal injury

Although inflammation of the MPF triad in isolation impacts fetal outcomes, many pathogens also have a more direct pathophysiology in the fetus, crossing into fetal circulation after invading the placenta [72,86]. Some pathogens, including CMV, LCMV, ZIKV and Toxoplasmosis, have a predominant neurotropism, invading the fetal CNS [11,72,101]. The detrimental effects on embryonic and fetal brain structures are likely via multiple different pathways. Dysfunction of progenitor neuronal and glial cell populations and their subsequent connections throughout the fetal neuroaxis may result from first trimester pathogen invasion. In vitro studies of cultured neural progenitor cells have shown that ZIKV infection induces necrotic apoptosis, abnormal centrosome function, mitotic dysfunction, and reduced proliferation [102]. Proteomic studies of neural cell progenitors infected by CMV, ZIKV and Toxoplasmosis have shown that these pathogens lead to modification of normal protein expression, notably by upregulating proteins useful for pathogen replication and downregulating proteins related to neural development and proliferation [11]. In a murine model, neural progenitor cells in the subventricular zone of the anterior forebrain and the subgranular zone of the dorsal forebrain were preferentially affected, with evidence of apoptosis and decreased cell proliferation [103]. ZIKV has also been shown to infect human microglia in *in vitro* studies, which was associated with an increased inflammatory profile in these cells; local brain inflammation in response to infection may thus cause additional injury [104]. Some pathogens, such as B19V and Syphilis, may cause CNS issues in the fetus via secondary effects from fetal anemia and thrombocytopenia causing hypoxic or hemorrhagic injury to the developing brain [72].

6.4. The neural exposome and long-term effects of congenital infections

The human *exposome* involves time-dependent gene-environment interactions that represent health or disease expression. The exposome encapsulates the totality of environmental exposures over an individual's lifetime as well as the impact of accumulated toxic stressor exposures that can adversely affect the developing and aging nervous system [105,106]. Negative life course effects of the exposome from the fetal period through adulthood can be expressed through genetic variation and epigenetic modifications contributing to neuroimmunogenic changes that influence the disease-susceptibility before and beyond reproductive senescence. Neurologic sequelae ranging from childhood developmental disorders and epilepsies to adult-onset cerebrovascular, neurodegenerative, mental health and cognitive disorders are maladaptive phenotypic expressions of the neural exposome. These later adverse outcomes also involve prenatal disease pathways associated with congenital infections. For example, in the context of the COVID-19 pandemic, studies have linked the exposome to immune factors influencing the risk for SARS-CoV-2 infection as well as illness severity [107,108]. Fetal exposure to pathogens and systemic inflammation from MIA, IPS and FIR can be interpreted using the *reproductive, pregnancy and placental exposomes* that contribute to genetic susceptibility throughout the lifespan. As discussed previously, MIA in rat models has been shown to induce epigenetic changes and modifications in gene expression in offspring [83]. Similarly, proteomic analysis in neonates expressing FIR demonstrate changes in production of pro-inflammatory molecules and in gene expression [90]. In utero inflammation and infection appears to be associated with alterations in fetal immune system development as well as *reprogramming* of the fetal immune cells through epigenetic changes which may be associated with short- and long-term susceptibility to disease [75]. The impact of multiple exposomic effects, mediated by exposure to maternal infection and inflammation, on long-term outcomes should not be underestimated.

6.5. Congenital infections and public health policy

Congenital infections and their consequences need to be assessed through the lens of public health priorities by addressing the impact of health disparities in healthcare on the risk for neurologic diseases [105] as well as congenital defects [109]. Various congenital infections have different incidence rates between low- and middle-income countries (LMIC) and high-income countries (HIC) countries, and also vary depending on health disparities within the same country. For example, a study of seroprevalence for *Toxoplasma gondii* in Brazil was found to be significantly correlated with socio-economic status (SES) – 23 % in a group with higher SES and 84 % in a group with lower SES – likely associated with access to treated and filtered water [110,111]. A seroprevalence study in Kyrgyzstan reported that seropositivity was increased with urban living and with lower SES in the rural population [112]. Even in the United States, seropositivity has been shown to increase significantly based on racial and ethnic identification (Black and Mexican American), birth outside of the United States, and SES [113,114]. Similarly, Black and Mexican American women of childbearing age in the United States were shown to have a significantly higher incidence of CMV infection [115] and higher CMV seropositivity [116] than non-Hispanic white women. A lower SES was also significantly correlated with incidence of CMV infection in a US cohort [115]. CMV seropositivity worldwide appears to be higher in South America, Africa and Asia (compared to Western Europe and the United States), lower in individuals identifying as white, and higher in people of lower SES [117]. Interestingly, in an Australian cohort of pregnant women and children, CMV seropositivity was higher in individuals from a lower SES, however rates of congenital CMV were higher in the group with the highest SES [118]; acquiring seropositivity before child-bearing age may be, in a sense, protective for future offspring. More recently, during the ZIKV epidemic in Brazil, the incidence of CZS and ZIKV-related microcephaly was significantly higher in the Northeast region, which has the highest poverty index in the country [119,120]. The incidence of CZS was significantly correlated with SES, poverty index, garbage management, sanitary installations, and access to clean water [109–121]. When considering public health education interventions, survey data show, for example, that general knowledge regarding Toxoplasmosis in the United States is lower in people with lower educational attainment and in non-white individuals [122].

When designing vaccination interventions for congenital infections, one must consider vaccine uptake in various populations. For example, a Canadian study analyzing rubella seropositivity (usually through childhood vaccination programs) in pregnant women found that rates of seronegativity – and thus lower vaccination uptake – could be correlated with markers of SES, including lower education status and, in a specific subgroup, household income [123]. Management of congenital infections must thus incorporate targeted health disparities in health care that reduce effective interventions for specific subsets of individuals who reach reproductive age. Public health measures and community education must promote medical equity beginning with reproductive

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health before conception. Pregnancy planning is paramount for people of all ethnicities and their partners. Specific high-risk groups include women with complex childhood medical diseases, those experiencing poverty and lack of access to health care, post-ovulatory adolescents, and women testing positive for sexually transmitted diseases [9,124].

7. Pathogens with peripartum or postnatal onset

Various pathogens can be transmitted from the mother to the infant during the peripartum period, either while in utero or during parturition, with clinical symptoms developing after birth. These pathogens are outside the scope of the current article and have been reviewed elsewhere [125,126].

8. Conclusion

Congenital infectious encephalopathies are an important etiology for multiple neurologic sequelae of the developing brain. Unfortunately, infectious exposures are often not completely avoidable during pregnancy given limitations in reproductive health care delivery, pregnancy planning, and pregnancy surveillance with effective testing protocols. Congenital infections should be included in the differential diagnosis for a range of fetal-neonatal neurological conditions. These infections have non-specific as well as unique aspects to their presentation, diagnosis, and effects on the maternal-placental-fetal triad.

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