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The Impact of Maternal Infection on the Neonate

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Abstract

Maternal infection is a common occurrence during pregnancy, with a substantial impact on the infant. Some infections result in impaired development *in utero* and even death of the fetus. Other infections may be insidious in the mother but result in growth impairment and hearing loss in the infant. A growing body of evidence suggests that even infections such as chorioamnionitis, thought to have no long-term impact on the infant, may alter fetal development. This chapter will review congenital infections and their impact on neonatal outcomes, as well as newer findings suggesting that acute infection may result in adverse changes in the infant. We will explore novel mechanisms of pathogenesis and virulence, as well as areas that continue with ongoing research.

Keywords: pregnancy, infection, neurodevelopment, chorioamnionitis, TORCH infections, Zika

1. Introduction

Maternal infections during pregnancy can have a direct impact on the developing fetus and in some infections can result in fetal demise. It is extremely important to screen women for infections when it is available and practical and to treat when necessary. The current screening tests recommended by the American College of Obstetricians and Gynecologists include rubella, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), Group B streptococcus (GBS), tuberculosis and sexually transmitted infections including syphilis, chlamydia, and gonorrhea if risk factors are present [1]. The incidence of congenital infections in infants varies, with syphilis increasing dramatically from 639 cases in 2016 to over 1300 cases in 2018 in the United States [2]. Additionally, congenital cytomegalovirus, varicella zoster virus and herpes simplex virus diagnoses have increased over the last five decades [3]. Rubella has decreased since the introduction of Rubella immunization; prior to utilization of the immunization, over 100,000 infants were born worldwide with congenital rubella syndrome (CRS). By 2014, a 95% decrease in cases of CRS was observed in countries that followed the immunization schedule [4]. Thus, it is critically important that research efforts continue to prioritize the development of immunizations and treatments plans for all viruses that can result in congenital fetal infection in an attempt to minimize the substantial long-term morbidities that result.

2. Chorioamnionitis/intra-amniotic infection (IAI)

Chorioamnionitis is the term that has been used for decades to describe infection and/or inflammation of the chorion, amnion, or both. This has been further delineated into a “clinical” diagnosis based on maternal symptoms, and a “histological” diagnosis based on the pathology of the placenta following delivery. Clinical signs and symptoms are used to diagnose clinical chorioamnionitis, and include maternal fever, uterine fundal tenderness, maternal and/or fetal tachycardia and purulent amniotic fluid [5]. The most common bacterial organisms to cause chorioamnionitis are *Ureaplasma urealyticum* and *Mycoplasma hominis*. Histological chorioamnionitis is diagnosed by observing neutrophil infiltration into the chorion and amnion [6]. The variation in the definition of chorioamnionitis has resulted in confusion in neonatal management as well as difficulty in assessing the long-term impact of chorioamnionitis on development. Therefore, intra-amniotic infection (IAI) has been developed to replace the prior diagnosis of chorioamnionitis [7].

IAI was updated in 2017 by the American College of Obstetricians and Gynecologists into three categories which are readily diagnosed. Isolated maternal fever (IMF) is the first category, in which the mother has a single intrapartum temperature of $\geq 39.0^{\circ}\text{C}$ or a temperature of $38.0\text{--}38.9^{\circ}\text{C}$ that persists for 30 min, with treatment recommendations including the consideration of broad-spectrum antibiotics [7, 8]. Given the numerous potential causes of maternal fever, the utilization of antibiotics is at the providers’ discretion. Suspected IAI is diagnosed when the mother has an elevated temperature ($\geq 39.0^{\circ}\text{C}$) or a slightly elevated temperature ($38.0\text{--}38.9^{\circ}\text{C}$) along with one of the following risk factors: maternal leukocytosis, purulent cervical drainage or fetal tachycardia [7, 8]. Confirmed IAI is diagnosed with a positive amniotic fluid test or placental pathology demonstrating histologic evidence of infection [7]. Similar to the previously used histological chorioamnionitis, a criticism of this diagnosis is that it is made after the clinical situation has resolved, and thus does not aid in the acute management of the mother or the infant. Both suspected and confirmed IAI diagnoses should result in treatment with intrapartum antibiotics and antipyretics [7].

IAI is present in nearly 50% of very early preterm birth [9], after which multiple complications can occur and a wide array of neonatal morbidities and mortalities are observed. This has led to speculation that IAI is directly impacting the fetal and neonatal development and outcomes, as well as potentially resulting in preterm birth, which then impacts development and outcomes. The majority of studies that have investigated this question utilized diagnoses of chorioamnionitis, which included both clinical and histological cases. Given the variation of diagnoses included in these studies, it is not surprising that the results have also been varied. A large study of 2390 extremely preterm infants (born <27 weeks’ gestational age) from sixteen centers across the United States found infants exposed to histological and clinical chorioamnionitis had an increased risk of cognitive impairment at 18–22 months’ corrected age [10]. A separate study of 350 infants found that while gestational age was significantly lower among those with exposure to histological chorioamnionitis, there was no association with intraventricular hemorrhage, white matter injury around birth, or differences in cognitive or motor outcomes at 18–24 months’ corrected age [11]. Additional studies have found weak causal or associative roles of chorioamnionitis with cerebral palsy risk [12] and no increased risk of white matter injury on magnetic resonance imaging (MRI) following histological chorioamnionitis in premature infants [13]. Additional investigation is required with the new IAI definitions to determine if there are consistent findings with developmental outcomes in those diagnosed with IAI.

3. TORCH infections

TORCH infection is a mnemonic that has classically been used to describe congenital infections that can impact fetal development. In the past, TORCH represented Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19 and newer pathogens such as Zika), Rubella, Cytomegalovirus and Herpes Simplex Virus. However, as more pathogens are being discovered and the “other” category is expanding, some experts feel the mnemonic is not as relevant today.

3.1 Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan which typically causes mild illness in most immunocompetent individuals [14, 15]. While a large portion of infected children and adults are asymptomatic, Toxoplasmosis is considered one of the major causes of death linked to foodborne illness in the United States. If an immunocompromised individual, pregnant woman, or fetus/infant acquires the infection, there can be severe, even fatal, consequences [14, 15]. Illness can range from non-specific systemic symptoms such as fever, lymphadenopathy and hepatosplenomegaly to congenital toxoplasmosis (CT), which is classically described as a triad of chorioretinitis, intracranial calcifications and hydrocephalus. CT can lead to loss of vision and hearing, decreased cognitive function, and neurodevelopmental delay if untreated [14, 16–18].

T. gondii exists in three forms: tachyzoite, bradyzoite, and sporozoite. The definitive hosts are members of the *Felidae* family, but warm-blood mammals can also serve as intermediate hosts [17]. Felines can acquire *T. gondii* through the ingestion of tissue cysts containing bradyzoites in infected prey or through the ingestion of oocysts containing sporozoites in anything contaminated with feces from an infected cat. They can excrete un-sporulated oocysts in their stools 3–30 days after infection and can shed for 7–14 days. If in the right climate (such as warm and humid), the oocysts can sporulate for 1–5 days, after which they can remain infectious for years. If the tissue cysts found in intermediate hosts or the sporulated oocysts are ingested by humans, they transform into active tachyzoites. The tachyzoites then primarily infect the central nervous system, eyes, musculoskeletal system, and placenta by infecting nucleated host cells to bypass the blood brain barrier and placental barricade. Incubation is 7 days with a range of 4–21 days [14, 15, 18].

For pregnant women who have an acute infection with *T. gondii*, the timing can be crucial and dictates the treatment course. Typically, the earlier in pregnancy that acute infection occurs, the lower the rate of transmission to the fetus. Unfortunately, there is an increased severity of illness if transmission occurs earlier in the pregnancy [14, 15]. The reverse is true for infection later in pregnancy (such as during the third trimester), during which there is a high rate of transmission but with less severe illness in the fetus.

The diagnosis of primary or latent infection is made primarily using serologic tests. Toxoplasma-specific Immunoglobulin G (IgG) and Immunoglobulin M (IgM) can be performed routinely at non-reference laboratories. Any positive IgM results are then submitted to reference laboratories that can perform additional testing for confirmation [18]. If a pregnant woman is found to have acute infection, then an amniocentesis can be performed, and the fluid can be sent for polymerase chain reaction (PCR) testing. If the PCR is negative and the fetus is believed to have not acquired the infection, the next best step is treatment in the mother with spiramycin in an attempt to prevent transmission [14, 15, 17, 18]. If, however, the fetus is thought to be infected, then the mother is started on a combination of

pyrimethamine, sulfadiazine, and folinic acid. Spiramycin, a primarily bacteriostatic macrolide that has activity against some gram-negative and gram-positive organisms as well as some spirochetes, is unable to cross the placenta whereas the combination of anti-parasitic medications can cross the placenta and thus can aid in treatment of the fetus [18, 19]. The combination is also used for fetal infection confirmed at or after 18 weeks of gestation or maternal infection acquired during the third trimester [14, 17, 18]. As untreated CT can lead to fetal demise or death within the first few days of life, and chorioretinitis can develop in a significant proportion of infants whose mothers were untreated, it is imperative to diagnose and start treatment in a timely manner [18].

Once an infant with suspected CT is born, he or she should be thoroughly examined and evaluated. Serologies, a complete blood count (CBC), hepatic function tests, blood PCR, urine PCR, cerebrospinal fluid (CSF) PCR, and CSF studies including glucose level, protein, and cell count, should be sent [18]. The newborn should also have ophthalmologic, auditory, and neurologic evaluation including imaging of the brain [18]. Infected infants should receive treatment regardless of any clinically apparent symptoms, as a large proportion of infants with asymptomatic CT at birth go on to develop visual/hearing impairment, learning disabilities, and psychomotor delay [15, 16, 18, 20]. Treatment consists of the same anti-parasitic combination of pyrimethamine, sulfadiazine, and folinic acid [18, 19]. If CSF studies show an elevated protein concentration (greater than 1 g/dL) or there is evidence of severe chorioretinitis, then a corticosteroid such as prednisone is added until there is a decrease in protein concentration in the CSF or resolution of severe chorioretinitis [15, 18, 19]. Treatment is continued at least through 12 months of age, with consideration of shorter treatment duration for infants who remain asymptomatic for the first three months of life [18, 19]. For those infants who are asymptomatic with positive Toxo-specific IgG but negative IgM and Immunoglobulin A (IgA), there should be repeat IgG testing every four to six weeks until disappearance of IgG. There is no clear consensus on the treatment of these infants [18, 19].

Studies looking at the outcomes of infants with CT have shown significantly better neurologic and developmental outcomes in those that were treated than those who were not [21]. It is important to note that compared to their uninfected siblings, the children that received treatment had a lower level of cognitive function though there was no deterioration over time. In terms of ophthalmologic outcomes, it was found that when followed up to 22 years of age, new ocular lesions could be detected in adolescence which points to the importance of continued ophthalmologic evaluation.

3.2 Other: syphilis, varicella-zoster, parvovirus B19, Zika

3.2.1 Syphilis

Treponema pallidum, a thin, motile spirochete, is the organism that causes syphilis [18], a sexually transmitted infection that can also result in congenital infection to a fetus. While there was initially a decline in the cases of syphilis observed in the United States in 2000–2001, an alarming resurgence has recently been noted. There has been an increase of 72% in the number of reported primary and secondary cases in the United States from 2013 to 2017, with the number of congenital syphilis cases increasing more than 150% from 2013 to 2018 [22–24]. It is thought that the increase in methamphetamine use, having sex with a person who injects drugs, injection drug use and heroin use are the primary factors that are leading to this dramatic increase in syphilis cases [22, 25].

Acquired syphilis is typically divided into three stages: primary, secondary and latent. During the primary stage, painless indurated ulcers form on the skin or mucous membranes of the areas exposed and heal spontaneously in a few weeks. The secondary stage, typically 1–2 months after the primary stage, is characterized by a maculopapular rash that typically includes the palms and soles, lymphadenopathy and mucocutaneous lesions including condylomata lata [18]. Finally, the latent stage occurs when there are no clinical signs or symptoms of infection, but an individual remains seroreactive [18]. *T. pallidum* can infect the central nervous system (CNS) during any stage, resulting in neurosyphilis. Transmission to the fetus during pregnancy can occur at any point, with primary and secondary syphilis having the highest rates of transmission at 60–100% [18].

It is recommended that all women be screened for syphilis early in pregnancy with a nontreponemal test, with repeat testing later in pregnancy for high risk individuals. These tests include the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma reagin (RPR) test [18]. These nontreponemal tests utilize an antigen that reacts in the presence of antibodies (to syphilis). However, given that the antigen is not specific for syphilis and is a component of cell membranes, false positives may result from other infections including varicella and measles, or by tissue damage observed in connective tissue disease and even pregnancy itself [26]. Therefore, a positive nontreponemal test should be followed by a confirmatory test such as fluorescent treponemal antibody absorption (FTA-ABS) or *T. pallidum* particle agglutination (TP-PA) tests. Additionally, any person found positive for syphilis based on screening and confirmatory testing should also be screened for human immunodeficiency virus (HIV) given the high rate of co-infection.

Treatment for syphilis is parenteral penicillin G; if an individual is allergic to penicillin G, they should undergo desensitization due to the lack of proven efficacy of alternative agents in this setting. Lack of treatment during pregnancy can result in stillbirth and neonatal death in nearly 40% of women with primary and secondary stage disease, 40% of infants being infected and only 20% of infants being healthy and uninfected [27]. Additionally, fetal infection can result in anemia, hepatomegaly and hydrops [24]. Treatment of the infant should not be delayed, as early treatment may prevent neurologic sequelae [24].

A serological diagnosis is made on the infant if the nontreponemal titer (VDRL or RPR) is fourfold higher than that of the mother (both samples should be obtained around the same time), if the nontreponemal titer persists or increases after birth, or if the treponemal antibody titer (FTA-ABS or TP-PA) remains positive at 12–18 months of age. The choice of test on the infant is dependent on the test that the mother had received, as the titers will need to be compared [18]. A complete evaluation, including complete blood cell count (CBC), liver function tests, obtaining cerebrospinal fluid (CSF) to test for VDRL reactivity, ophthalmologic examination and long-bone radiographs to assess abnormal ossification, radiolucencies or dislocation of epiphyses is then needed [28]. Neuroimaging should be considered if there are any concerns for central nervous system involvement [18]. Ten days of treatment with parenteral penicillin G is typically used in infected infants, with close follow up required. Titers should be repeated by 3 months of age and noted to be declining, with nonreactivity noted by 6 months of age [28]. If the mother received appropriate treatment that was administered >4 weeks before delivery, and the infant has a normal physical examination with the titer equal to or less than fourfold the maternal titer, then no evaluation is recommended. However, inadequate treatment in the mother should result in evaluation of the infant and treatment with penicillin G for 10 days [28].

Clinically, nearly half of infants do not have any apparent signs of infection, although bone lesions and hematologic and hepatobiliary abnormalities may be

present, with hepatomegaly one of the most common findings [24, 29]. Infants that develop symptoms may have rhinitis in the first week of life, in which persistent white discharge (“snuffles”) occurs which contains spirochetes [29]. Additional symptoms can include generalized lymphadenopathy and a maculopapular rash [29]. Long term outcomes of infants not appropriately treated can include sensorineural hearing loss, interstitial keratitis, secondary glaucoma, corneal scarring, vision impairment, Hutchinson teeth (smaller teeth that are widely spaced with notches), saber shins (sharp anterior bowing of the tibia), frontal bossing, saddle nose, gummas (soft, non-cancerous growth) and scarring [29]. Life-long disabilities can occur in congenital syphilis infections if infants are not appropriately screened and treated [28].

3.2.2 Varicella-zoster

Varicella-zoster virus (VZV) is a herpesvirus that is transmitted by respiratory droplets, direct contact with skin lesions, and transplacentally during pregnancy [30]. Infants that are exposed to VZV during the last few weeks of pregnancy may develop neonatal varicella which can be quite severe; congenital varicella syndrome (CVS) develops in infants exposed during the pregnancy, with the risk being highest if the exposure occurs in the first trimester [30]. Infants exposed after 20 weeks’ gestation only have about 2% chance of developing CVS [31]. Infants with CVS most commonly have skin lesions in a dermatomal distribution followed by neurologic defects, eye disease and skeletal anomalies [31]. Neurologic defects can include cerebral cortical atrophy and ventriculomegaly. Unfortunately, CVS is fatal in about 30% of cases within the first month of life [32].

The monovalent vaccine approved in 1995 and the quadrivalent vaccine introduced in 2005 have impacted the prevalence of congenital infection as seroprotection is nearly 100% after 2 doses of the vaccine [18]. Thus, at this time, CVS is considered an extremely rare disorder.

3.2.3 Parvovirus B19

Human parvovirus B19 is a nonenveloped, single-stranded deoxyribonucleic acid (DNA) virus with humans as the only host [18]. The virus replicates in erythrocyte precursors and is transmitted via respiratory tract secretions, exposure to blood or blood products, and vertically [18]. While it often causes a mild respiratory tract infection with a “slapped cheek” rash, it can be lethal to a fetus, with the risk of death being as high as 10% [33]. The incidence of parvovirus B19 infection during pregnancy is 3–4%, with the transplacental transmission rate approaching 30% [34]. Fortunately, approximately 50–75% of women of reproductive age are immune to parvovirus B19 [35]. The timing of infection during pregnancy does alter the risk of fetal death, with first trimester infections resulting in up to 71% risk of fetal loss [34]. The difficulty in diagnosing the virus during pregnancy arises in the lack of symptoms that most adults experience, and as many as 70% of women would have no symptoms if infected during pregnancy [34]. Arthropathies are one of the most common symptoms and should raise suspicion for possible infection [34]. Additionally, the presence of fetal ascites or pericardial effusions on ultrasound should trigger high suspicion as well [33].

Fetal hydrops, or abnormal accumulation of fluid/edema in two or more compartments, is common in the setting of Parvovirus B19 infection, with a meta-analysis finding a 9.3% pooled incidence, as well as an increased risk of fetal loss, spontaneous abortion and stillbirth [36]. Parvovirus B19 is among the most common causes of non-immune fetal hydrops, and while spontaneous resolution of infection

can occur, only about 5% of cases with hydrops will show spontaneous resolution of the infection with disappearance of hydrops on follow up ultrasounds [37].

Severe anemia and thrombocytopenia occur *in utero* following parvovirus B19 infection, along with myocardial dysfunction [38]. These factors together are likely the etiology of the fetal hydrops. *In utero* transfusions (IUT) are often necessary and reduce mortality rates when compared to expectant management. A meta-analysis found IUT was performed in 78% of hydropic fetuses compared to 29% of non-hydropic fetuses, with the difference likely due to the hydropic fetuses at higher risk of demise [37]. Complications may occur in up to 5% of cases, especially if the fetus is likely more sensitive to vascular overload [38]. Thus, intrauterine exchange transfusions (IUET) have also been attempted in cases of fetal hydrops in the setting of parvovirus B19 infection. Unfortunately, thus far it results in similar survival rates as IUT and does not seem to be clinically superior as a treatment modality [38].

Longer-term testing reveal abnormal neurodevelopment following intrauterine parvovirus B19 infections in those also diagnosed with hydrops. Brain abnormalities including parenchymal calcifications, venous infarction, arterial infarction, cerebellar hemorrhage, and cortical malformations including diffuse cortical dysplasia and polymicrogyria have been described in congenital parvovirus infections [39]. If there are no abnormalities on imaging and hydrops resolves prior to delivery, one study found normal neurodevelopment in survivors at 1- and 5-year follow-up [40]. While the overall risk of mortality and morbidity are high, there is the potential for a normal outcome in select cases of congenital parvovirus infections.

3.2.4 Zika

Zika virus, ZIKV, is an emerging flavivirus that first became apparent internationally after Brazil declared a national public health emergency in 2016 followed by the World Health Organization declaring the outbreak a public health event of international concern [41]. The virus was first identified in 1947 in Uganda, after which cases of human infection have been infrequent and fairly localized [41]. ZIKV is transmitted by infected *Aedes* spp. mosquitoes, sexual contact and blood transfusions [42]. Around 80% of ZIKV that occur in adults are asymptomatic, with other cases having a mild febrile illness, headache, rash, fever and conjunctivitis [42]. However, severe neurologic sequelae can also occur in adults.

Congenital Zika syndrome (CZS) is variable in the presentation and severity with only a subset of infants that were exposed having apparent signs and symptoms at birth [41]. Infants exposed to ZIKV *in utero* are expected to survive, however a severe phenotype can result, particularly when exposure occurs in the first trimester [43]. ZIKV replication in brain tissue can continue after birth, and thus infants that are initially asymptomatic may develop symptoms within the first year of life [41]. The phenotype of CZS appears to consist of severe microcephaly and possibly a partially collapsed skull, thin cerebral cortices with subcortical calcifications, macular scarring, congenital contractures and marked early hypertonia [41]. Microcephaly is the most common symptom, occurring in up to 91% of CZS, and is often severe with the mean occipitofrontal head circumference falling 3–4 standard deviations below normal [43]. Both the central and peripheral nervous systems are impacted, with resultant effects on musculoskeletal, auditory and ophthalmologic systems and symptoms including conductive hip dysplasia, abnormal posturing of extremities, conductive hearing loss and abnormalities of the retina and optic nerve [43]. Up to 55% of infants with CZS have structural ocular abnormalities, making visual screening and interventions critically important to occur early in life to allow for neuroplasticity optimizing the outcomes [44]. This has led to the

recommendation of any infant with suspected CZS or exposure to ZIKV to have an ocular examination before hospital discharge and again at 3 months of age [44].

A meta-analysis of 42 articles revealed the most common brain abnormalities following ZIKV exposure *in utero*, including decreased brain volume, increased extra-axial cerebrospinal fluid space, subcortical calcifications, microcephaly, ventriculomegaly, malformation of cortical development, basal ganglia calcifications, and mega cisterna magna [45]. These findings support the concept that ZIKV interferes with normal neuronal migration during development which then impacts the brain development. The major neuronal migration is occurring before the 25th week of gestation, making exposure to the virus in the first and second trimesters the most devastating. Infants with ZIKV exposure and no apparent congenital syndrome are also at risk for abnormal neurodevelopmental outcomes, as evidenced in a recent study of 70 infants followed to age 18 months [46]. These infants had confirmed exposure to ZIKV but no findings to support CZS, and despite the normal head circumference, had subsequent neurodevelopmental deficits develop over the first year of life [46]. As studies continue and longer-term outcomes become known, it is critically important to follow any infant with ZIKV exposure closely.

3.3 Rubella

Rubella is caused by a single stranded ribonucleic acid (RNA) virus which is highly contagious and only transmitted between humans [18, 47]. It is usually spread through respiratory droplets and in most cases will result in a mild viral disease. Symptoms may include fever, rash, malaise and adenopathy. The virus is able to infect cells of the respiratory tract and then spread via the systemic circulation to multiple organ systems, including the placenta [48]. When the infection occurs during pregnancy the virus can be transmitted to the fetus and result in death of the fetus or a range of congenital anomalies known collectively as Congenital Rubella Syndrome (CRS) [18]. The timing of when a pregnant woman contracts the virus appears to be related to the risk of congenital infection and fetal defects. Studies estimate that maternal infection occurring during the first 12 weeks of gestation has roughly a 90% chance of congenital infection with the risk of defects nearly 85% [49]. When congenital infection occurs during the first trimester, hearing defects, heart defects, neurologic damage, and ocular defects appear more commonly. CRS is a combination of these defects but most classically is described as a triad of cataracts, congenital heart disease, and sensorineural deafness [49, 50]. Other manifestations include intrauterine growth restriction (IUGR), hepatomegaly, splenomegaly, thrombocytopenia and dermal erythrocytosis (commonly known as a “blueberry muffin rash”) [18].

Pregnant women in the United States are tested for rubella immunity by serologic screening. Those who have had a natural infection or have received at least one dose of the rubella vaccine tend to have lifelong immunity [18]. Those women who are found to be non-immune should receive one dose of the vaccine after childbirth, as vaccination during pregnancy has theoretical teratogenic risks due to the vaccine being live [18]. If a pregnant woman is exposed to the rubella virus, they should have serologic testing for rubella-specific IgM and IgG. If she is found to have rubella-specific IgG, then she is considered immune. However, if there is no IgG detectable at the time of exposure then convalescent serologies are obtained 3 and 6 weeks after exposure, with IgG reactivity at these time points indicating a recent infection [18]. Unfortunately, there is no treatment for rubella outside of supportive measures.

When congenital infection is suspected, diagnosis can be done by testing for rubella-specific IgM in fetal blood or detection of the virus in amniotic fluid [49].

Postnatally, an enzyme-linked immunosorbent assay (ELISA) can also be done for rubella-specific IgM. If positive, then confirmatory testing is done by reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs, urine, or oral fluid [47, 49]. In some infants the virus can be detected in nasopharyngeal secretions and urine for over a year [18, 49]. While there is no treatment for CRS, diagnosis is important in terms of follow up. Due to the risk of cataracts among other ocular abnormalities (including microphthalmia, glaucoma, chorioretinitis), hearing loss, neurologic manifestations (such as developmental delay, autism), and endocrine disorders (including diabetes, thyroid disease) children with CRS must be evaluated periodically for management of these potential complications [48–50]. The introduction of the vaccine has resulted in a significant decline in cases of rubella infection and CRS in the United States, with an average of 14 reported rubella cases a year and 4 CRS cases a year from 2001 to 2004 [51].

3.4 Cytomegalovirus

Cytomegalovirus (CMV) is a double stranded deoxyribonucleic acid (DNA) virus that is universally found and generally causes mild or subclinical symptoms in most children and adults [18, 52]. It can be transmitted via contact with infected secretions, transfusion of blood products from infected donors, organ transplants from infected individuals, or vertically [18]. When it is vertically transmitted, CMV has the potential to cause severe and permanent sequelae [18, 52, 53]. CMV is known as one of the most common congenital viral infections and is the leading, non-genetic cause of sensorineural hearing loss in children in the United States [18]. It can be transmitted to the fetus by crossing the placenta, through contact of infected cervical secretions during birth, or perinatally by ingestion of breast milk containing the virus [18]. When CMV is transmitted *in utero*, it can be due to primary maternal infection during pregnancy, reactivation of a prior infection, or reinfection with a different strain despite presence of maternal antibodies [54, 55]. Reactivation and reinfection are more common than a primary infection; however, the latter tends to cause more severe sequelae especially if infection occurs earlier in pregnancy.

Of those infants whose mother had an acute infection during pregnancy, 30–40% will have congenital CMV (cCMV) [18, 55]. Infants with cCMV are symptomatic in 10–15% of the cases, with half to two-thirds of these infants developing sensorineural hearing loss (SNHL) later in life [55]. Symptoms at birth can include thrombocytopenia, hepatomegaly, splenomegaly, microcephaly, periventricular calcifications in the brain, chorioretinitis, hepatitis, and SNHL. Long term outcomes include progressive SNHL and neurodevelopmental delay [18, 53, 55]. Of the infants who are asymptomatic at birth, around 15% will later develop SNHL [18]. Imaging of the fetal brain can be completed *in utero* via transvaginal ultrasound or with magnetic resonance imaging (MRI). cCMV can result in germinolytic cysts, lenticulostriate vasculopathy, temporal lobe and occipital cysts as well as cerebellar hypoplasia and migrational disorders including polymicrogyria [52]. Periventricular calcifications is the most frequently reported finding on brain imaging of cCMV cases, impacting 34–70% of diagnosed patients [56].

Testing during pregnancy is not routinely done, but serologic testing can be performed if a pregnant woman has been exposed or is suspected of having CMV infection. CMV-specific IgM has low specificity as it can persist for 6–9 month following primary infection and can also be detected during reactivation [54]. CMV IgG avidity index however can be used to confirm primary infection; avidity testing is a method to measure the strength of the bonding between antibodies and the virus. Low avidity would indicate recent infection while high avidity takes time to

occur and would indicate a past infection. There is no current recommended treatment for acute CMV infection during pregnancy [18, 54].

There is also no current routine testing for CMV in infants. Some states have mandated targeted CMV screening for those who fail their routine newborn hearing screen, however it is important to note that targeted screening will miss those newborns who are asymptomatic at birth but still at risk for developing SNHL later in life [18]. For symptomatic infants, the diagnosis of cCMV can be made postnatally if testing is done within 3 weeks of birth as to avoid the difficulty of differentiating between intrauterine and perinatal infection [18, 54, 57]. CMV can be isolated from the urine, saliva, respiratory secretions, blood, or cerebrospinal fluid [18]. Viral cultures, rapid shell vial cultures, and PCR can be completed [54]. Treatment for those infants who are symptomatic regardless of CNS involvement includes intravenous ganciclovir or oral valganciclovir [18, 54, 58]. The latter is preferred due to ease of administration as duration of treatment is six months. If there are concerns for abnormal gastrointestinal absorption due to other factors, treatment can be started with IV ganciclovir [54]. Studies have found that those who have antiviral treatment started within the first month of life have significantly improved audiologic and neurodevelopmental outcomes at 12 and 24 months of age compared to those who do not [53]. Treatment with either valganciclovir or ganciclovir can cause significant neutropenia; absolute neutrophil counts should be monitored weekly for the first six weeks of treatment, followed by screening at eight weeks of treatment, and thereafter monthly for the duration of treatment [54]. Infants with mild symptoms or isolated SNHL are not recommended to receive antiviral treatment at this time due to lack of data in this population [54].

Long term outcomes to consider in children with cCMV include SNHL and neurodevelopmental delay. These children should have frequent audiologic assessments as SNHL can develop and/or progress after the newborn period [54]. While there are no established universal guidelines for hearing evaluation, studies indicate that screening should continue for at least the first four years of life after which late-onset SNHL is seldom seen.

3.5 Herpes simplex virus

Herpes simplex viruses are large, double-stranded DNA viruses with two types, HSV-1 and HSV-2 [18]. Traditionally, HSV-1 can cause vesicular lesions in areas above the waist while HSV-2 involves areas below the waist. It is, however, becoming increasingly more common to see genital HSV-1 lesions. Both types are able to cause herpetic disease in neonates when acquired from the mother. Transmission can occur during the birthing process via contact with genital lesions, an ascending infection, intrauterine, or postnatally from contact with lesions [18, 52]. A primary genital HSV infection in the mother near delivery has 10–30 times the risk of transmission compared to a recurrent infection. This is thought to be due to lower concentrations of transplacental HSV antibodies in the neonate [18, 59]. Unfortunately, defining an infection as primary versus recurrent may not be straightforward, as women can be asymptomatic and may be unaware that they have had a prior infection with HSV. Furthermore, viral shedding can occur in the absence of clinical symptoms [59].

If a pregnant woman does have genital lesions characteristic of HSV near delivery, then swabs of the lesions can be sent for viral culture and PCR with serologic testing to determine the type. From these results, women can be classified into four different categories: documented first primary infection, documented first episode non-primary infection, assumed first episode (primary or non-primary), or recurrent infection (see **Table 1** adapted from Kimberlin et al.).

CLASSIFICATION	CULTURE OR PCR	HSV-1 ANTIBODY	HSV-2 ANTIBODY
DOCUMENTED FIRST PRIMARY INFECTION	Positive	Negative	Negative
DOCUMENTED FIRST EPISODE NON-PRIMARY	Positive for HSV-1	Negative	Positive
	Positive for HSV-2	Positive	Negative
ASSUMED FIRST EPISODE (PRIMARY OR NON-PRIMARY)	Positive for HSV-1 or HSV-2	Unknown	Unknown
	Negative or unknown	Negative or unknown	Negative or unknown
RECURRENT INFECTION	Positive for HSV-1	Positive	Negative
	Positive for HSV-2	Negative	Positive

Table 1. *Diagnostic tests for Herpes simplex virus (HSV) Antibodies and Culture/PCR. This table describes the classification of HSV infection based on culture or PCR test results as well as HSV-1 and HSV-2 antibody test results.*

Women classified as having a primary infection or first episode can be treated with oral acyclovir for 7–10 days [18]. Those with a recurrent episode can be treated with the same or higher dose for 5 days [18]. If a woman has a known history of HSV then suppressive therapy should be started at 36 weeks' gestation to decrease the risk of recurrence at delivery, although this will not entirely suppress shedding [60]. Other preventative methods include avoiding invasive fetal monitoring, such as fetal scalp electrodes, and opting for elective cesarean sections when lesions are present at the time of delivery [52, 60].

Neonatal HSV can have different manifestations. SEM disease includes disease of the skin, eyes and/or mouth; 45% of infants with HSV will have SEM. Another 30% of infants with HSV will have localized central nervous system (CNS) disease with or without skin involvement. The remaining 25% of infants with HSV will have disseminated disease which can involve multiple organs, most commonly the liver and lungs [18]. The onset of disease varies between the different manifestations, with SEM disease presenting at 5–11 days of life, CNS disease presenting between 8 and 17 days of life, and disseminated disease presenting between 10 and 12 days of life [61]. Initial symptoms may be non-specific and include feeding difficulties, lethargy, seizures, suspected sepsis, vesicular rash or severe liver dysfunction, with as many as 30% of infected neonates not having skin lesions [52, 60]. As there can be high morbidity and mortality rates in newborns with HSV, it is imperative to diagnose and initiate treatment as soon as it is suspected [18].

Guidelines have been published on the management of asymptomatic neonates born to women with active genital lesions [59]. In newborns whose mothers have a history of genital HSV prior to pregnancy and present with active lesions at delivery, there is a low risk of transmission. However, the infant should still have surface swabs of the mouth, nasopharynx, conjunctivae, and anus obtained for culture and PCR as well as serum HSV PCR sent at 24 h of life. Waiting to send samples until 24 h of life ensures that any positive results would represent active viral replication in the infant and not maternal contamination [59]. Intravenous acyclovir is not started in this situation unless the infant becomes symptomatic, or the surface swabs and/or serum are positive. This would confirm infection and require a lumbar puncture to obtain cerebrospinal fluid (CSF) for PCR testing. The result of the CSF PCR is key in determining treatment duration. If the CSF and serum HSV PCR are negative, then empiric IV acyclovir is administered for a total of 10 days to prevent progression from infection to disease. If the CSF PCR is positive, then treatment should

be administered for 21 days [59]. After the treatment course has completed, a repeat lumbar puncture is necessary in cases of CNS disease to document clearance. If the repeat CSF HSV PCR is still positive, then acyclovir is continued for another 7 days. A repeat lumbar puncture is obtained to show clearance. This process is repeated until the CSF is negative. Any infant who undergoes a treatment course for HSV disease should have suppressive therapy with oral acyclovir for 6 months after the completion of parenteral treatment (see **Figures 1** and **2**) [59, 62].

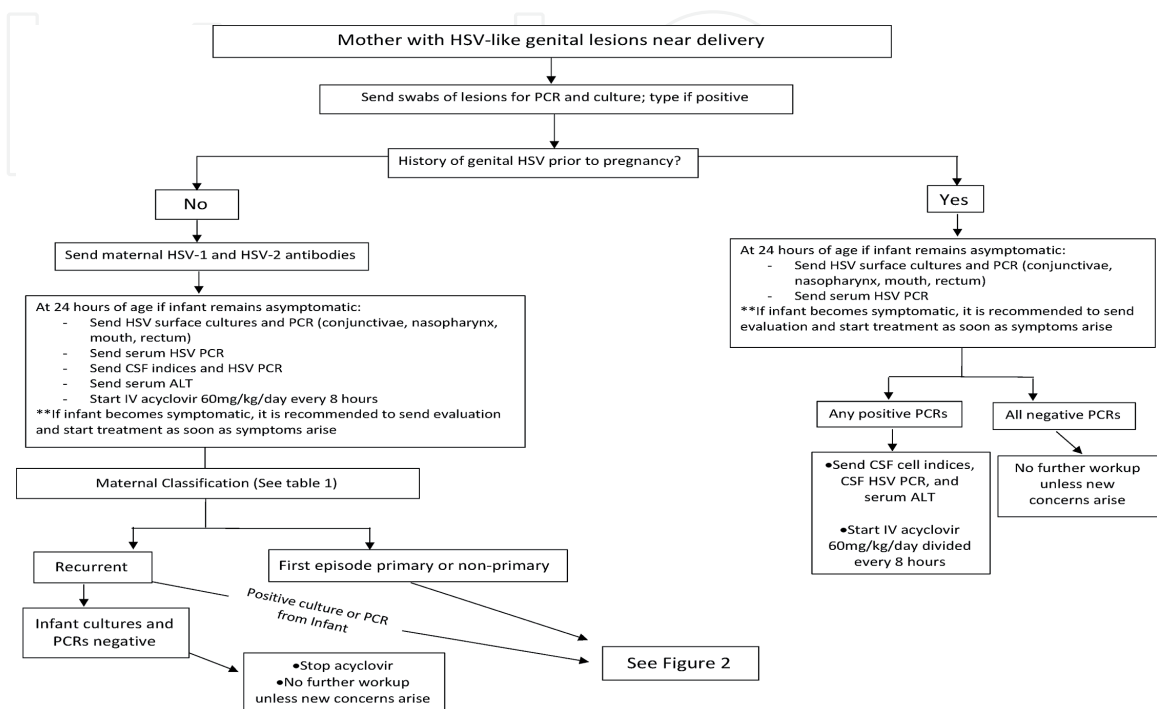


Figure 1. Infant evaluation in suspected exposure to Herpes simplex virus (HSV). This flow diagram, adapted from Ref. [59], describes the infant evaluation(s) to complete if there was concern for maternal HSV infection around the time of delivery due to the presence of lesions.

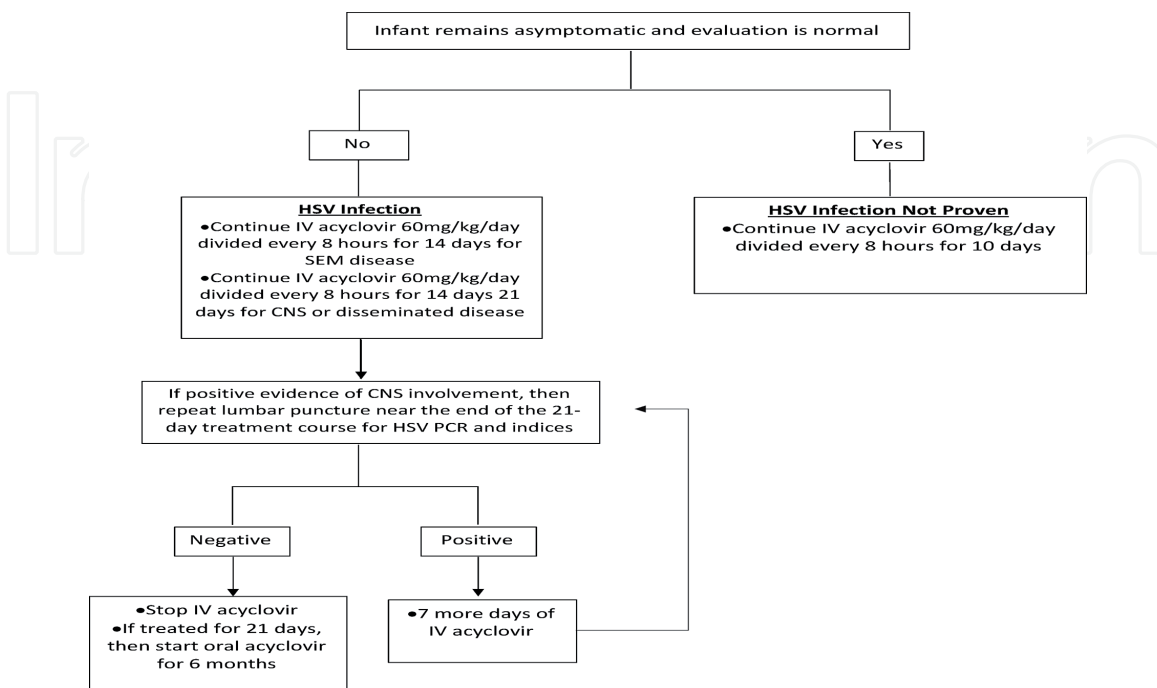


Figure 2. Infant treatment recommendations for suspected congenital Herpes simplex virus (HSV) infection. This flow diagram, adapted from Ref. [59], describes treatment regimens based on infant symptoms.

In the case that an asymptomatic neonate is born to a mother with active genital lesions but does not have a history of genital HSV prior to pregnancy, then the importance lies in distinguishing whether it is a primary, non-primary or recurrent infection [59]. The mother should not only have the swabs sent for PCR testing and culture but should also have serum serological tests performed for HSV-1 and HSV-2 antibodies. The infant requires evaluation at 24 h of life with HSV surface cultures and PCR testing of the serum and CSF. The CSF samples should also be sent for cell count and chemistries, with screening serum alanine aminotransferase obtained. IV acyclovir would be started empirically after obtaining the samples at 24 h of age while awaiting results. Once the maternal testing is resulted, maternal classification can then be determined as shown in **Table 1**. If the mother is deemed to have a first episode primary or non-primary infection, then treatment of the infant would include 10 days of IV acyclovir for a normal evaluation (infant remains asymptomatic, negative CSF and serum HSV PCR, normal CSF indices, and normal serum ALT), 14 days for an abnormal evaluation (positive serum HSV PCR, symptomatic infant, or abnormal ALT) and 21 days for CNS infection (positive CSF PCR or abnormal indices) [59]. A neonate with a positive CSF HSV PCR, regardless of the maternal classification, would be managed as described above for HSV disease. It is important to note that if the infant becomes symptomatic at any point, even prior to the testing obtained at 24 h of life, then immediate evaluation and treatment should be initiated [59]. Other risk factors that may prompt testing and treatment prior the 24 h include: prolonged rupture of membranes (>4–6 h) and prematurity (≤ 37 weeks' gestation) in the setting of maternal genital lesions characteristic of HSV [59].

Only 10% of infants survive in untreated HSV disseminated disease with 50% of infants surviving in untreated HSV CNS disease [61]. Inadequately treated or untreated HSV SEM disease can progress to either disseminated or CNS disease; those that survive have a significant proportion that show some neurologic sequelae, namely in the form of motor, speech, and developmental delay [61]. Outcomes, especially mortality, improve the earlier that treatment is initiated, making it imperative to evaluate and begin empiric treatment whenever HSV infection is suspected [61]. Oral suppressive therapy has also been shown to improve neurodevelopmental outcomes at 12 months of age compared to those that did not receive long-term antivirals, suggesting that ongoing neurologic injury may occur in infants affected by HSV disease [62].

4. Additional viruses

A review of additional viruses that can impact infants exposed during pregnancy is provided below. These viruses have been associated with a range of adverse outcomes in infants with prenatal/perinatal exposure, however they remain uncommonly diagnosed or the impact on the fetus remains extremely varied. However, given the increased risk of potential adverse outcomes, they are briefly discussed.

4.1 Hepatitis E

The hepatitis E virus (HEV) is a single-stranded RNA virus which is known as a major cause of acute viral hepatitis especially in developing countries through ingestion of contaminated water sources [18, 63]. While it generally causes a mild illness in most adults, pregnant women tend to have more severe disease. Mortality has been observed in pregnant women, especially if infected with genotype 1 [18, 63]. HEV is estimated to be responsible for up to 3000 stillbirths a year in

developing countries and can commonly cause preterm delivery in infected mothers with resultant poor neonatal outcomes [63, 64]. When HEV is transmitted vertically, hepatitis can be present from birth and persist throughout the infant's life but is not known to be associated with congenital anomalies.

4.2 Enterovirus

Enteroviruses are a group of RNA viruses that can spread between humans via respiratory routes, vertically, and fecal-oral transmission [18]. Symptoms in adults and children can be varied and may include respiratory, dermatologic, neurologic, ocular, cardiac, muscular, and gastrointestinal manifestations [18]. When enterovirus is transmitted vertically or more commonly peripartum, the neonate may remain asymptomatic without sequelae or have severe symptoms including septic shock with multiorgan dysfunction [65]. There is limited evidence to suggest that infection with enterovirus during pregnancy is associated with congenital anomalies or fetal death [65].

4.3 Congenital lymphocytic choriomeningitis virus syndrome

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus spread by rodents which can cross the placenta; rarely it can be transmitted during delivery by exposure to maternal secretions or blood and cause congenital viral infection [66–68]. Infected pregnant women can have non-specific viral symptoms and may report direct exposure to or the presence of rodents in their homes [66, 68]. Common findings in an infant affected by LCMV are macrocephaly or microcephaly and ocular abnormalities; additionally, neurological abnormalities may be present and include hydrocephalus, periventricular calcifications, seizures, neurodevelopmental sequelae including intellectual disability, or even death [67, 68]. These symptoms suggest a similarity with other congenital infections previously discussed, such as CMV or toxoplasmosis, which may contribute to an underestimation of the prevalence of LCMV when congenital infection is suspected [66, 68].

4.4 West Nile Virus

The West Nile Virus (WNV) is a flavivirus that was initially isolated in 1937 and did not reach the United States until an outbreak in 1999 [69–71]. The primary mode of transmission is through the bite of an infected *Culex* species mosquito, with individuals ranging from no symptoms to 0.7% of infected individuals developing neuro-invasive disease with encephalitis, meningitis or acute flaccid paralysis possible [69]. There is no specific treatment or vaccine at this time [70]. Case reports of infants born to mothers with WNV have shown an array of outcomes, with follow up at 2–3 years of age not consistently showing any developmental delays [69]. Findings have included chorioretinitis, white-matter loss and cystic changes, and congenital defects such as lissencephaly, polydactyly, aortic coarctation and cleft palate [69]. Additional studies on the impact of infants with exposure during gestation, and longer-term outcomes are needed to truly delineate if WNV results in congenital anomalies.

4.5 Adenovirus

Human adenoviruses (HAdV) are DNA viruses in the Adenoviridae family, with 7 subgroups and 52 serotypes [72]. While typically the cause of a “cold”, the severity

of illness can range from mild to severe with gastroenteritis, pneumonia and neurologic disease possible [73]. Reports have not noted any specific fetal malformations, although infants with positive polymerase chain reaction (PCR) testing had a higher incidence of neural tube defects and echogenic liver lesions with and without hydrops [74].

5. Conclusion

Many of the maternal infections that previously resulted in significant impact and poor outcomes on the developing fetus have improved as treatments and vaccines have been introduced and refined. However, other pathogens are now becoming more apparent in their impact on fetal development, such as Zika virus. Some infections are declining in incidence, with a resultant decrease in congenital infections (such as the nearly 80% decline in Rubella infections) [51]. Other infections are continuing to increase, with the true impact on society yet to be determined. Thus, it is imperative that we monitor any infections in a pregnant woman, and complete a thorough examination and evaluation of each infant born with the hopes of identifying any abnormalities quickly and improving the outcomes of each infant to the best of our ability.

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