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Gender-specific effects of viral infections may be the result of differences in pathophysiology, differences in exposure or risk factors, and effects specific to pregnancy. Although these differences have been noted for many years, for most infections the exact mechanisms behind gender-specific differences have yet to be elucidated. This chapter will examine the following:

1. Gender-specific manifestations of viral infections resulting from differences in pathophysiology
2. Gender-specific manifestations of viral infections resulting from differences in exposures or risk factors
3. Manifestations specific to pregnancy

I. Human Lymphotropic Viruses: HTLV-1 and HTLV-2

The first human retrovirus, human T-cell lymphotropic virus type 1 (HTLV-1) was discovered in 1979, derived from the lymphocytes of a patient originally thought to have an aggressive form of cutaneous T-cell lymphoma. Two years later, HTLV-2 was isolated from the cells of a patient with atypical hairy cell leukemia. Morphologically, HTLV-1 and HTLV-2 are type C viruses, which make up a group of retroviruses known as the primate T-cell leukemia/lymphoma virus. Both are single-stranded RNA viruses with a genome that undergoes reverse transcription into a DNA provirus that integrates into a host T-cell genome. This integration process allows the retrovirus to cause lifelong infection, evade immune clearance, and produce diseases of long latency.

There is 65% overall nucleotide homology between HTLV-1 and HTLV-2. Based on sequencing data, HTLV-1 is composed of three types: Cosmopolitan, Melanesian, and Zairian, which are present in widely scattered populations in the world. Two best-studied areas are the islands of southwestern Japan and the Caribbean basin. HTLV-1 infection has also been reported in central and West Africa, Melanesia, and parts of South America and the Middle East. HTLV-2, however, consists of type A, B, and C and is reported mainly in intravenous drug users and their sexual contacts. Endemic areas include the United States, Europe, South America, and Southeast Asia. HTLV seroprevalence can range from 5–30%, depending on the population in question, but clinical disease develops in only about 3–5% of carriers of HTLV-1 over their lifetime.

There is a wide range of clinical conditions linked to HTLV-1. The best-described associations include adult T-cell leukemia/lymphoma (ATL), a proliferative disorder of T-cells characterized by lymphadenopathy, hypercalcemia, lytic bone lesions, skin involvement, and hepatomegaly. HTLV-1 has also been linked to the HTLV-associated myelopathy or tropical spastic paraparesis (HAM/TSP), a chronic neurologic syndrome associated with demyelination of the long motor neurons of the spinal cord.

Other HTLV-1 associated clinical syndromes include infective dermatitis, polymyositis, uveitis and arthritis, Sjögren syndrome, and infiltrative pneumonitis. HTLV-2 does not have any clearly documented disease associations other than a link to HAM/TSP. It has been associated with atypical hairy cell leukemia and mycosis fungoides, yet there is no clear evidence confirming an etiologic role of HTLV-2 in these disorders. Routes of transmission of HTLV-1 and HTLV-2 are similar and include sexual intercourse, administration of blood products, and mother-to-child transfer.

Laboratory diagnosis of infection rests on an enzyme-linked immunosorbent assay (ELISA) screen; there is, however, cross reactivity between HTLV-1 and HTLV-2 in the assay, and the virus subtype is distinguished by Western blot. Polymerase chain reaction (PCR) assay to quantify the level of virus is used in research settings.

A. Manifestations Specific to Pregnancy

In endemic areas, seropositive persons are clustered around families, reflecting predominance of mother-to-child and male-to-female transmission. Breast-feeding is the predominant route of vertical transmission and occurs through ingestion of infected milkborne lymphocytes. According to epidemiologic studies from Japan, 15–20% of children of seropositive mothers acquire HTLV-1 through breast-feeding [1], whereas only 1–2% of bottle-fed infants of mothers positive for HTLV-1 become infected. Transmission appears to increase with the number of months that the infant has nursed. Recent data from Japan suggest that babies who were short-term breast-feeders (for 6 months or less) showed a statistically significant lower seroconversion rate than long-term breast-feeders: 3.9% vs 20.3% [2,3].

There may be other factors implicated in the mother-to-child transmission. Two separate studies from Japan and France identified maternal anti-HTLV-1 antibody titer and maternal HTLV-1 proviral load as additional risk factors; higher levels of both were associated with increased risk of HTLV-1 seropositivity in children [4,5].

The antibody titers correlate with the proviral burden. This may explain the paradoxical finding of high antibody titers among women who transmit HTLV-1 to their infants through prolonged breast-feeding; transplacental maternal antibodies appear to protect the infant from infection in the first months of life, but subsequently the infants become infected via maternal virus transmitted in breast milk.

Intrauterine transmission occurs rarely; the placenta can be infected by HTLV-1, but the infection does not reach the fetus.
The placenta has been known to be a barrier against intrauterine transmission, perhaps by mechanism of apoptosis; it has been reported that the incidence of apoptosis-positive cells in placentas from pregnant women who were HTLV-1 seropositive was higher than that from women who were HTLV-1 seronegative [6]. HTLV-2 is also found in breast milk, and although there are no good studies of mother-to-child transmission, the finding that seropositive children had seropositive mothers supports this route of infection.

B. Gender-Specific Manifestations Resulting from Differences in Exposure or Risk Factors

HTLV-1 seroprevalence is characterized by an age-dependent increase that is similar in diverse geographic areas. Among children, the prevalence rate of both sexes is low, about 1%, and the male-to-female ratio is 1. Starting with adolescence, however, the prevalence increases and infection rates between males and females diverge, with female rates exceeding male rates. This trend continues into adulthood, and whereas male rates plateau by the age of 40 years, female rates continue to increase and peak at about age 60 years [7]. The reason for this divergence is ascribed to the fact that although sexual transmission is bidirectional, male-to-female transmission occurs 10 times more efficiently. For example, some studies report that after 10 years of sexual contact with an infected partner, a woman has a 61% likelihood of being infected, as opposed to only 0.4% for a man [8]. In a Japanese cohort study of 100 discordant couples practicing unprotected sexual intercourse, there were seven seroconversions during 5 years of observation. Uninfected females were 3.9 times more likely to become infected than uninfected males [9].

Similar differences in prevalence were noted among pregnant women. A study of young pregnant women (<30 years old) in French Guiana demonstrated that factors such as high gravidity, high parity, and a negative Rhesus factor were independently linked to an increased risk of HTLV-1 seropositivity [10]. It has been postulated that the increase in HTLV-1 prevalence rates in the younger than 30 age group could be the result of high levels of sexual transmission in this population. In Jamaica or French West Indies, for example, women who were HTLV-1 seropositive were slightly more likely to have had more than three lifetime sex partners, earlier age at first sexual intercourse, and a history of sexually transmitted diseases [10–12]. In many studies an increased risk of seropositivity has been seen with increasing age but also with prior miscarriages, caesarian sections, and high gravidity. These factors are known to be associated with a low socioeconomic level, and they could reflect sexual activity and a high number of lifetime sexual partners [10]. Sexual transmission of HTLV-2 has been difficult to study.

C. Gender-Specific Manifestations

HTLV-1–associated myelopathy, or tropical spastic paresis, affects mainly adults, with a female-to-male predominance of 3:1. It has been shown that HAM/TSP incidence increases with age and is higher in women between 40 and 59 years of age compared with men in the same age group. With HTLV-1 infection, the lifetime risk of developing HAM/TSP was estimated to be 1.9% overall and is slightly higher in women (1.8%) than in men (1.3%) [13]. Thus, the higher prevalence of HTLV-1 in women living in endemic areas does not fully explain the preponderance of female HAM/TSP, suggesting that other cofactors may be present. It has been postulated that the overrepresentation of females and the increase in incidence with age are indicative of the predominance of infections acquired through sexual transmission [13,14].

HTLV-1 infection is also considered a risk factor for ATL. A male predominance in ATL has been shown to exist in Japan, perhaps because of an earlier average age of infection among males. The overall ATL mortality was shown to be higher for males than females. Reasons for this difference have not been elucidated [15].

II. Polyomavirus

Human polyomaviruses, JC and BK, named after patients from whom the initial virus isolates were obtained, were first isolated in 1971. Polyomaviridae family, which are unenveloped icosahedral nucleocapsids with a double-stranded DNA genome.

They are worldwide in distribution, and approximately 60–80% of adults in United States and Europe have antibodies to JC or BK virus. The infection is acquired in childhood, persists in the kidneys, and is asymptomatic in the majority of patients. The seroprevalence of both viruses increases sharply during childhood. The route of transmission is not known, and the only detailed information about transmission comes from studies of nonprimate agents. The BK and JC viruses have been detected in human and mice tonsillar tissue as well as murine intestinal endothelial cells, suggesting oral or respiratory mode of transmission. Clinically, primary infection in childhood is largely asymptomatic and only rarely associated with upper-respiratory or urinary tract disease. Following primary infection the viruses remain latent in the kidney. Both BK and JC viruses can be detected in mononuclear cells in peripheral blood, bone marrow, and the central nervous system (CNS).

Reactivation of infection occurs most commonly with immunosuppression, and viral shedding increases with age and levels of immunosuppression. The BK virus has been linked to ureteral stenosis and hemorrhagic cystitis in renal or bone marrow transplant recipients; however, the majority of renal transplant recipients with JC or BK virus viruria have no symptoms. JC virus has been shown to have tropism for oligodendrocytes and to cause progressive multifocal leukoencephalopathy in older patients with underlying hematologic malignancies and in patients with HIV.

BK and JC viruses are slow growing in tissue culture, which hampers isolation of the virus from clinical specimen. Cytologic examination of urinary epithelial cells, looking for intranuclear inclusions, can be used to detect BK and JC virus viruria. PCR, however, is the most sensitive method of detecting BK or JC virus in the cerebrospinal fluid (CSF) and in the urine.

A. Manifestations Specific to Pregnancy

Asymptomatic viruria with JC and BK virus occurs primarily in immunosuppressed patients and pregnant women; in humans with intact immune function it is a rare occurrence. The high
seroprevalence of JC and BK virus antibodies in the absence of seroconversion in pregnancy suggests that viral excretion represents reactivation of previously acquired infection [15a]. About 5% of pregnant women demonstrate a fourfold rise in antibody titers to BK virus, and about 9–15% have a similar increase in JC virus antibody titers. Virus shedding occurs primarily during the third trimester of pregnancy and usually ceases in the immediate postpartum period [16,17]. Both JC and BK virus shedding may occur, although JC virus viruria is more common [17].

Pregnant women tend to have more severe manifestations of infections in which cell-mediated immunity is important. Compared to pregnant controls, women with reactivation of the virus tended to have a mononcytosis earlier in pregnancy, a lower neutrophil count, and a significant lymphopenia [7,16]. The only detailed data concerning polyomavirus transmission comes from nonprimate studies: perinatal transmission of virus can occur in mice if the mother develops a primary infection during pregnancy. At present there is no definitive evidence that perinatal transmission of polyomaviruses occurs in the setting of maternal viruria. In one study immunoglobulin M (IgM) to BK virus was detected in three of six infants whose mothers had serologic evidence of BK virus infection during pregnancy [7]. However, more recent serologic studies have failed to demonstrate evidence of congenital infection by BK virus [18].

III. Parvovirus B19

Human parvovirus B19, a small, nonenveloped, single-stranded DNA virus, was first discovered in 1974 during evaluation of tests for hepatitis B surface antigen. This virus can be propagated only in human or primate erythroid cells. It is cytotoxic and in normal hosts has been shown to lead to an acute but self-limited cessation of red blood cell production. In immunocompetent children B19 is the cause of erythema infectiosum; in adults it may lead to acute symmetric polyarthropathy. In patients with underlying hemolytic disorders, infections lead to transient aplastic crises. In the immunocompromised host B19 viremia manifests as pure red-cell aplasia and chronic anemia, whereas in the fetus the virus can lead to death in utero, hydrops fetalis, or congenital anemia. Parvovirus B19 infection is prevalent throughout the world, and by the age of 15 years old the prevalence of antibody is quoted to be more than 50% [7].

Outbreaks of infections occur most commonly during late winter and spring, and the infection is probably spread by an airborne virus spread by droplets of infected respiratory-tract secretions. Patients are most infectious during the late prodromal phase when cough and coryza are at their peak.

The illness is characterized by a prodromal phase of malaise, cough, coryza, fever, and anorexia. Toward the end of the prodrome, Koplik’s spots appear on the buccal mucosa, preceding the onset of maculopapular rash. The entire illness lasts 7–10 days and the rash resolves.

Morbidity and mortality are highest in infants, the elderly, and patients of low socioeconomic status. Natural measles induces lifelong immunity, and reexposure is almost always asymptomatic [7]. In developed countries complications occur in only about 10% of cases; the most common ones include otitis media, pneumonia, acute disseminated encephalomyelitis, subacute sclerosing panencephalitis and inclusion-body encephalitis. Myocarditis, pericarditis, conjunctivitis, and keratitis can also occur.

Diagnosis is clinical; infection can also be documented by a fourfold increase in measles antibody titer in acute and convalescent serum. Treatment is supportive, and great emphasis is placed on preventive measures such as passive immunization of exposed persons within 6 days of exposure and active
immunization between the ages of 12 to 15 months and the second dose on school entry. Contraindications to measles vaccination include pregnancy.

A. Manifestations Specific to Pregnancy

In most countries, maternal antibodies confer protection against measles during the first 6 months of life and the disease may be modified by waning levels of antibody that persist for an additional 6–9 months [7]. Because vaccinated mothers have lower levels of antibody to the measles virus than do mothers who have had natural measles, these infants will become susceptible to measles at an earlier age.

Postnatally acquired neonatal measles is rare. The high prevalence of passively acquired maternal antibodies results in protection of most newborns. In the absence of maternal antibodies, measles in the neonate is often a severe disease with the majority of deaths associated with pneumonia.

Measles, unlike rubella (German measles), does not cause congenital abnormalities in the fetus. There have been, however, reports of spontaneous abortion and premature delivery [7]. Passive immunization with immunoglobulin is recommended at birth for infants born to women with active disease.

Maternal antibody levels have obvious implications for infants’ immunity and timing of vaccinations. Measles antibody titers are lower in women vaccinated as children than in women who have had natural measles, and the children of vaccinated women lose transplacentally acquired measles antibodies before 1 year of age. Therefore vaccination can be routinely given as early as 12 months of age because most women of childbearing age were vaccinated as children.

The morbidity and mortality of measles are higher in pregnant women mostly because of an increased risk of measles virus pneumonia during the third trimester and puerperium [22].

Interstitial pneumonitis resulting from viral replication and inflammation in the lower-respiratory tract is more severe in pregnancy [23]. For example, during a resurgence of measles in 1989–1991, a number of pregnant women developed measles. Out of 50% of those who required hospitalization, 54% had respiratory complications (primary measles pneumonia) requiring admission to an intensive care unit. There was one death in this group [22]. Likewise, during a 1951 epidemic in Greenland, pregnant women had 4.8% mortality compared to 1.0% mortality in nonpregnant women. Death was associated with left-ventricular failure and pulmonary edema [7].

V. Mumps

Mumps virus is a member of the Paramyxoviridae family, and its virion is an irregularly shaped spherical particle with a single-stranded RNA genome. Mumps is a disease of school-aged children and has a worldwide distribution. It is commonly acquired at school and spread to susceptible family members. Infection is rare in infants younger than 1 year old, presumably as a result of passively acquired maternal antibodies. The virus is transmitted via direct contact, droplet nuclei, or fomites and enters through the nose or mouth; the peak period of contagion is at the onset of parotitis. The virus replicates in the epithelial cells of the upper-respiratory tract and is spread to regional lymph nodes; primary viremia follows during which the virus is seeded to parotid glands, the CNS, pancreatic tissue, and seminiferous tubules. The clinical syndrome develops after an incubation period of 16–18 days; symptoms may be nonspecific at first, soon followed by tenderness and enlargement of the parotid gland. CNS involvement is the most common extrasalivary manifestation of mumps, but clinical meningitis or encephalitis occurs in only 0.1–10% cases [8]. Complications of infection include epididymoorchitis, oophoritis, pancreatitis, migratory polyarthritis, and (rarely) myocarditis or hearing loss.

Diagnosis is made on the basis of a history of exposure followed by parotid swelling and parotitis. Laboratory confirmation may be obtained by documenting an increase in IgM antibodies. The virus can also be isolated from the saliva, the CSF, or urine of infected patients. Mumps can be efficiently prevented by use of the Jerryl Lynn strain of live mumps vaccine. It is administered as part of the measles–mumps–rubella vaccine and is given in two doses. It is contraindicated in pregnant women or in significantly immunocompromised patients.

A. Gender-Specific Manifestations

Symptomatic gonadal involvement occurs in 25–38% of postpubertal men and is rarely documented in women. Some reports note that up to 5% of postpubertal women develop oophoritis [7]. Ovarian involvement may be underdiagnosed because unless a careful pelvic examination is documented, abdominal and pelvic pain may be attributed to pancreatic infection. Symptoms include fever, nausea, vomiting, and abdominal pain. Impaired fertility and premature menopause, albeit rare, have been reported [7]. About 15% of females infected with the virus complain of breast swelling and tenderness, and the incidence of mastitis doubles among postpubertal women [7].

Mumps was the most common cause of encephalitis in the United States until 1975. Although men and women have the same frequency of development of parotitis, CNS involvement (encephalitis or meningitis) has a clear male predominance (threefold).

B. Manifestations Specific to Pregnancy

Maternal infection during the first trimester can lead to bloodborne infection of the placenta and ultimately to fetal wastage. A proliferative necrotizing villitis with decidual cells containing intracytoplasmic inclusions has been described in the products of spontaneous and induced abortions [24].

Siegel and Fuerst have documented that second- and third-trimester mumps infections were not associated with increased fetal mortality [25]. Although there is no clear connection between mumps infection during pregnancy and congenital defects, there may be a possible association between mumps during the first trimester and low birth weight.

Mumps virus is excreted in breast milk, but few cases of prenatal mumps have been described [8]. However, transplacental transfer of maternal neutralizing antibodies has been clearly demonstrated and accounts for the rarity of mumps in young infants as well as lack of response to immunization in this age group. Antibody titers in maternal and cord serum are identical [26].
VI. Alphaviruses

The alphaviruses are RNA viruses in the Togaviridae family that are mostly mosquitoborne and cause a wide range of diseases in humans and animals. The main target organs are muscle, brain, reticuloendothelial system, and the joints. Serologically these viruses can be divided into six antigenic complexes: Eastern Equine Encephalitis (EEE), Venezuelan Equine Encephalitis (VEE), Sindbis (western equine encephalitis, or VEE, virus is the most notable one), Semliki Forest (Chikungunya and Ross River virus are notable human pathogens), Barmah Forest, Middleburg, and Ndumu antigenic complex. Clinically, these viruses can be divided into those that are associated with fever, rash, and polyarthritis (Chikungunya virus, Ross River virus, and O’nyong-nyong virus are the most important ones) or those that are associated with encephalitis. Alphaviruses are limited in their geographic spread by the range of their respective arthropod vectors. EEE virus infection, for example, occurs along the eastern and Gulf coasts of the United States; some cases have been documented in South America and Canada. VEE viruses are distributed primarily in states west of Mississippi and in corresponding Canadian provinces, whereas VEE infection has been documented primarily in South and Central America, reaching Texas. Infections secondary to encephalitis-causing alphaviruses are manifested by headaches, high fever, nausea, and vomiting; respiratory symptoms may occur as well.

There is no specific treatment for any of the alphavirus infections. Prevention depends primarily on control of vector mosquito populations.

A. Manifestations Specific to Pregnancy

Alphaviruses can be transmitted transplacentally in mice as well as humans. In mice, the virus infects the placenta, where it persists and spreads to the fetus despite the development of maternal antibody. The timing of maternal infection has implications for the fetus. In humans no fetal abnormalities were observed in infants infected with Ross River virus at 11–19 weeks of gestation; however, earlier infection has lead to fetal death [27].

Infections with the VEE virus have been associated with increases in spontaneous abortion [28] associated with cerebral necrosis and calcifications similar to those seen in toxoplasmosis. Infections acquired early in pregnancy have been associated with fetal hydrencephaly, porencephaly, and cerebral dysgenesis. Similarly, transplacental transmission has been documented for VEE, resulting in perinatal infection within the first week of life.

B. Gender-Specific Manifestations

VEE in older children and adults shows a male preponderance: male patients are two to three times more likely to develop disease than are female patients [29]. In contrast, there are some data that among alphaviruses associated primarily with polyarthritis and rash, the Ross River virus may show a female preponderance of polyarthritis [30,31].

VII. Viral Respiratory Infections: Coronavirus, Parainfluenza, Respiratory Syncytial Virus, Adenovirus, and Rhinovirus

A. Gender-Specific Manifestations

Gender does appear to influence the severity of respiratory syncytial virus (RSV) infection. There are epidemiologic data from Chapel Hill, North Carolina, to suggest that boys younger than 6 years of age had a higher rate of RSV lower-tract disease: 2.4 per 100 compared with 1.5 per 100 for girls. The greater severity of infection in male children is suggested by the preponderance of boys admitted to the hospital with lower respiratory–tract disease [8].

Similar data were derived from the Cleveland Family Study, an investigation conducted from 1948 to 1957 that followed almost 100 families to identify common respiratory illness. The investigators found that the highest number of illnesses occurred in young children, and they were the most likely introducers of infections. Mothers were the next most likely common introducers. More recent studies conducted in Michigan focused again on the family and demonstrated that illnesses were more frequent in boys than in girls up to 3 years of age. After the age of 3 years old, the incidence became more frequent in females. Females between ages 20–29 years had a greater increase in frequency in total respiratory illnesses compared to males.

Another relevant observation emerging from these studies was that women who did not work outside the home had higher rates of respiratory illness than women who worked out of the home. Overall, women working out of the home still had a higher frequency of illness than males [32–34].

VIII. Varicella-Zoster Virus

Varicella-zoster virus (VZV) is the virus that causes chickenpox (varicella) and shingles (zoster). VZV is a member of the Herpesviridae family and the alpha subfamily, which also includes herpes simplex virus types 1 and 2 and herpes B virus. Like all herpesviruses, it induces lifelong latency in the host. Initial infection with VZV leads to the clinical syndrome of chickenpox in most susceptible hosts, although infection can be subclinical, especially in young children. Primary VZV infection in adults tends to be a more severe illness than in children, and in individuals with impaired cell-mediated immunity fatal outcomes can be seen. After primary infection, latent VZV can be demonstrated in the dorsal root ganglia. Prior to an outbreak of shingles, VZV reactivates in the dorsal root ganglion and travels down the sensory nerves to the skin, where it causes the characteristic painful rash of shingles. Whereas chickenpox is primarily a disease of children, shingles is primarily a disease of adults. Decreased cell-mediated immunity puts individuals at increased risk of zoster, and outbreaks may be more severe and last longer than in nonimmunocompromised individuals. VZV infections occur worldwide and affect both sexes equally. Morbidity and mortality of primary VZV infection is more severe in adults than in children. Pneumonitis, the most frequent complication of varicella infection, is 25 times more common in adults than in children and accounts for most of the fatalities ascribed to VZV infection.
A. Manifestations Specific to Pregnancy

1. Maternal Effects

Primary varicella infection during pregnancy is associated with more severe disease than in other immunocompetent adults. In particular, the third trimester of pregnancy is associated with an increased risk of varicella pneumonitis and increased mortality. Before specific antiviral therapy was available for VZV, the mortality rate of varicella pneumonia was 11.4–15% in nonpregnant adults but increased to 36–41% in pregnant women [35]. Better supportive care and specific antiviral therapy have decreased this mortality to 13–14% [36], and more recent reports show further reductions [37]. Maternal smoking, 100 or more skin lesions, and the third trimester of pregnancy are associated with a higher risk of varicella pneumonia [38]. Because of these findings, varicella–zoster immune globulin (VZIG) is recommended as prophylaxis for pregnant women who are VZV seronegative who have had significant exposure to chickenpox. VZIG provides passive immunization against VZV and is effective in preventing or ameliorating disease in children. It is effective if given within 72 hours of exposure and may be effective if given up to 96 hours after exposure, but once disease is established, its efficacy is questionable. A new formulation of VZIG appears to result in higher maternal antibody levels and is comparable in efficacy and safety to standard VZIG. Acyclovir may also be used to protect against VZV infection and to treat established infection. Data on outcomes from 1129 prospectively followed acyclovir-exposed pregnancies (712 involving first-trimester exposure) were reported to a voluntary registry from June 1984 through December 1997. The data fail to show an increase in the number of birth defects identified among the fetuses exposed to acyclovir when compared with those expected in the general population. In addition, no pattern of defects was seen, suggesting that maternal acyclovir use in pregnancy is safe [39]. Varicella vaccine was licensed in 1995 to prevent chickenpox. Because it is a live-virus vaccine, its use is contraindicated in pregnancy. The Vaccine Adverse Event Reporting System (VAERS) had received 87 reports of inadvertent vaccination of pregnant women as of July 25, 1998. None of these exposures resulted in characteristic features of congenital varicella syndrome in the exposed fetuses [40]. It is interesting that 19 pregnant women received varicella vaccine by mistake (instead of VZIG) after chickenpox exposure, suggesting that health care workers need to be educated to eliminate confusion between these agents.

2. Fetal Effects

Maternal chickenpox in pregnancy can lead to fetal varicella in up to 10% of infections occurring before 24 weeks of pregnancy [41]. These infections are usually benign and self-limiting, but in up to 2% of cases occurring between 13 and 20 weeks of gestation, a characteristic constellation of findings known as the congenital varicella syndrome (CVS) may occur [42]. This syndrome is often severe and is characterized by skin lesions, limb hypoplasia, microcephaly, prematurity, chorioretinitis, mental retardation, and early death. Despite advances in the field, the syndrome remains difficult to predict. Negative PCR results for VZV in amniotic fluid is associated with a favorable outcome; however, a positive test correlates poorly with the development of CVS and it is not clear that the benefit of the test outweighs the risk of amniocentesis [41]. It is recommended that pregnant women who develop chickenpox during pregnancy be counseled about the risk of CVS.

Maternal chickenpox in the perinatal period can result in neonatal varicella infection, which is often severe and can result in mortality rates up to 30%. The risk is greatest to infants born 7 days or less after the appearance of maternal varicella because they receive a large transplacental viral inoculum without passive transfer of maternal antibody. Babies exposed to maternal varicella in the first 28 days of life also have increased risk of severe infections. VZIG is therefore recommended for all infants exposed to maternal varicella from 7 days prior to delivery up to 28 days after birth. Infants of mothers with zoster during the perinatal period are protected by maternal antibody and are not at increased risk of serious infection. Similarly, infants born to seropositive mothers who are exposed to chickenpox in their siblings are not at increased risk of serious infection.

IX. Cytomegalovirus

Cytomegalovirus (CMV) is a beta subgroup herpesvirus that is found all over the world and has infected almost all people by late adulthood. Although usually asymptomatic, primary CMV infection can be characterized by a mononucleosis-like syndrome of fever, lymphadenopathy, and lymphocytosis, especially in young adults. Like all herpesviruses, CMV establishes latent infection with polymorphonuclear cells, T cells, vascular tissue, renal cells, and salivary glands, all potentially harboring the virus. Reactivation, except in the case of immunocompromised individuals, is usually asymptomatic, and although reinfections can occur, they too are usually asymptomatic. Complications in the immunocompetent host are rare but can include pneumonia, hepatitis, Guillain-Barré syndrome, meningencephalitis, myocarditis, thrombocytopenia, and rash. Patients with the acquired immunodeficiency syndrome (AIDS) and bone marrow and solid organ recipients are at highest risk of complications from CMV infection. In patients with AIDS, CMV infection of the retina, CNS, and gastrointestinal tract are of particular importance. CMV has multiple different potential routes of infection. It is shed asymptomatically in saliva, urine, semen, and cervicovaginal secretions. Transmission can occur during intrauterine life, during the perinatal period, through breast milk, through close personal contact, through sexual intercourse, through blood transfusions, and through organ donation.

A. Manifestations Specific to Pregnancy

1. Maternal Effects

Symptomatic primary CMV infection is seen more commonly in pregnant women than in all other groups except for solid organ recipients [43]. In a study of a cohort of pregnant women with primary CMV infection, 59.8% had at least one clinical or laboratory manifestation and 31.4% had a flu-like illness or persistent fever [44], suggesting that it may be possible to diagnose infection in these patients. Fever, lymphadenopathy, splenomegaly, hepatitis, and atypical lymphocytosis are the
most common features of primary CMV infection in pregnant women.

2. Fetal Effects

CMV is the most common intrauterine infection affecting babies in this country. Congenital infection is most common in infants born to women with primary CMV infection during pregnancy. Preexisting maternal immunity results in a 69% reduction in the risk of congenital CMV infection [43]. Congenital infection occurs in approximately 30–40% of infants born to mothers with primary infection, and of these, about 10% will have clinical disease at birth [45]. Clinical disease includes varying degrees of cytomegalic inclusion disease, which may include jaundice; hepatosplenomegaly; petechial rash; multiple organ involvement; and CNS findings of microcephaly, chorioretinitis, and cerebral calcifications. Mortality with CNS involvement is high. Of the 90% of affected infants who are asymptomatic at birth, 5–17% will develop long-term sequelae including subtle effects on hearing and intelligence. Congenital infections resulting from recurrent maternal infection are much less severe as are postnatally acquired infections.

X. Epstein-Barr Virus

Epstein-Barr virus (EBV) is a member of the gamma herpesvirus family and is the etiologic agent of classic infectious mononucleosis. EBV infects B lymphocytes, which are also the site of latent virus infection [46]. EBV is found all over the world. Infection rates are highest in young children in developing countries; in the developed world approximately 50% of the population remains susceptible into the second decade of life [47]. Infection is spread through close personal contact, often with an asymptomatic shedder. In children younger than age 5 years, primary infection is usually asymptomatic but can present with upper-respiratory symptoms, pharyngitis, adenopathy, diarrhea, and abdominal complaints. In older children and adults, EBV primary infection often leads to classic infectious mononucleosis, which is characterized by malaise, headache, fever, pharyngitis, and cervical lymphadenopathy. Severe fatigue, nausea, vomiting, facial edema, and rashes can occur in more severe forms of the illness. Up to 90% of infected individuals will have mild hepatitis [48], and up to 50% will have splenomegaly. Serious complications found equally in either gender include airway obstruction from massive lymphoid hyperplasia, Guillain-Barré syndrome, facial nerve palsy, meningoencephalitis, aseptic meningitis, hemolytic anemia, pneumonia, myocarditis, pancreatitis, and glomerulonephritis.

A. Gender-Specific Manifestations

Splenomegaly is a rare but potentially fatal complication of EBV infection that occurs almost exclusively in young males [49]. The X-linked lymphoproliferative syndrome occurs in previously healthy males with a defect in the gene that encodes for signal transduction in T lymphocytes [50]. These individuals appear to have a selective immunodeficiency to EBV and when exposed, develop fulminant EBV infection. Bone marrow transplant, chemotherapy, and cord stem cell transplants are currently used to treat the disorder.

XI. Human Herpes Virus 8

This DNA gamma herpesvirus similar to Ebstein-Barr virus has been implicated in several important human neoplasms. The site of viral replication has not been completely elucidated, but viral DNA has been detected in saliva, semen, and peripheral blood mononuclear cells. Antibodies to this virus are found in diverse populations all over the world. Recently it has been isolated in tissues from all four forms of Kaposi’s sarcoma (KS): classic, iatrogenic, endemic African, and HIV-associated. KS is characterized by bluish-red, well demarcated, painless nodules in the skin, lungs, viscera and the biliary system [8,51]. Classically it occurs in elderly people, particularly men, of Mediterranean, Middle Eastern, or Eastern European descent. It has been recognized as an AIDS-associated malignancy particularly common among homosexual men infected with HIV-1. Other less common diseases it is associated with include primary effusion lymphoma arising exclusively in patients with AIDS or Castleman’s disease seen both in HIV-positive and HIV-negative patients.

A. Gender-Specific Manifestations

The epidemiology of KS reveals a male predominance of this disease; as mentioned earlier the classic, typically benign form of this disease is found predominantly in males. Incidence rates reported in Denmark, Sweden, and Wales are considerably lower in women than in males [52]. In the United States, a gender ratio of 4 was documented between 1970 and 1979. Similarly, HIV-seropositive homosexual and bisexual men are approximately 10 times more likely than the general healthy population to develop KS [51,53]. This suggests that gender may be a risk factor for development of KS.

Worldwide, occasional cases of classic KS have been reported in children, and among those cases data suggest male predominance. For example, a study of Tanzanian children before and during the AIDS epidemic reports 126 cases of KS. Of those children with pediatric KS, 126 (84%) were male and 24 (16%) were female. The gender ratio was 5.1:1 and 5.4:1 during the endemic and epidemic periods, respectively, and the highest occurrence of PKS was observed in the 0- to 5-years-of-age group [54].

XII. Human Herpesvirus 6

Human herpesvirus (HHV) 6 and HHV 7 are two lymphotropic viruses representative of the Roseolovirus genus within the Betaherpesvirinae subfamily. HHV 6 infects nearly all humans by the age of 2 years. It is found in circulating lymphocytes during primary infection, in monocyte-macrophages during the convalescent phase, or in healthy individuals. This virus has the capacity to persist in the human host; evades immune surveillance and can be transmitted very efficiently. Clinically it causes sixth disease, or roseola infantum, characterized by fever followed by a diffuse exanthem. HHV 6 has neurotropic and neuroinvasive properties. The virus has been found in the CSF of many children with aseptic meningoencephalitis (either as a sequela of sixth disease or independently) and in infants with febrile seizures [8].
A. Manifestations Specific to Pregnancy

Given the very high seroprevalence of HHV 6 in the first 2 years of life, both horizontal (via saliva) and vertical transmission have been implicated as the two possible mechanisms. Intrauterine transmission has been documented and the virus has been isolated in cord blood specimen. Interestingly enough, however, despite the high seroprevalence of infection among the general adult population, the rate of fetal HHV 6 or HHV 7 infection during pregnancy is less than 1% of all births [55,56]. Intrauterine transmission has been documented by HHV 6 DNA detection in cord blood samples of apparently healthy newborns and in fetuses following spontaneous abortions; however, no clear causation has been established. Because the viral genome has been documented in cervical swabs of about 20% of pregnant women, the possibility of intrapartum transmission has also been suggested [57].

Vertical transmission of HHV 6 may be symptomatic at birth; there are a few case reports in literature of early neonatal afebrile seizures resulting from a congenital HHV 6 variant B infection with subsequent neurologic impairments [58].

XIII. Influenza Virus

Influenza viruses belong to the family Orthomyxoviridae and are classified into three distinct groups—influenza A virus, B virus, and C virus—based on antigenic differences. The virus causes an acute, usually self-limited, febrile illness that occurs in outbreaks during winter months. Most common symptoms of fever, myalgias, and cough are often difficult to distinguish from symptoms caused by RSV, adenovirus, or other respiratory viruses [8]. Influenza attack rates are higher in children than adults, and pulmonary complications are more frequent in the elderly than in any other age group. CNS complications, specifically Reye’s syndrome, have been described following influenza in children.

A. Manifestations Specific to Pregnancy

Historical data from 1918 and 1957 pandemics have shown that severe influenza infections, with concurrent pulmonary symptoms, have resulted in a marked mortality in pregnant women and were associated with abortions, premature deliveries, and intrauterine growth delays. These data have not been confirmed in larger, case-controlled studies. There are some recent data as to whether maternal influenza infection in the second and third trimester of pregnancy can result in transplacental transmission or an increase in complications of pregnancy. One study in particular reported that although intercurrent influenza infection was found in about 115 of pregnancies, none of the cord sera from maternal cases were positive for virus-specific IgM antibodies; likewise IgG antibodies did not persist in any of the infants past 6 months after birth. Most importantly, there were no significant differences in pregnancy outcomes between cases and controls [59].

In psychiatric literature there is considerable discussion as to whether prenatal exposure to influenza is a risk factor for adult schizophrenia. In most epidemiologic studies, fluctuations in the incidence of influenza have been compared with the birth dates of patients with schizophrenia, based on the assumption that the risk of the mother being infected with the virus was associated with occurrence of an influenza epidemic during the pregnancy [60]. To date there is only one retrospective study that has attempted to answer this question. The study looked at more than 900 patients with schizophrenia born in France between 1949 and 1981, using nonschizophrenic siblings as controls, and documented that significantly more patients with schizophrenia than controls had been exposed to the virus during the fifth month of pregnancy [60]. Currently inactivated influenza vaccine is recommended for routine use in women who will be in the second or third trimesters of pregnancy. The basis for this recommendation is the high risk of exposure and disease resulting from influenza viruses in pregnant women as well as the impact of influenza virus infection on the fetus and infant derived mostly from historical data [61].

XIV. Rubella Virus

Rubella virus belongs to the Togaviridae family with its RNA genome, and it is closely related to alphaviruses. No vector is required for its transmission. Rubella is only moderately contagious, in contrast to measles, and the virus is spread in droplet forms. Infants with congenital rubella shed large quantities of the virus for many months. Persons who have been vaccinated do not transmit the virus to others.

Rubella virus causes an acute exanthemous infection in children and adults; symptoms include rash, fever, and lymphadenopathy and can cause birth defects following fetal infections.

A. Manifestations Specific to Pregnancy

Vaccines that are contraindicated because of the theoretic risk of fetal transmission include measles, mumps, and rubella [62], although the observed risk of congenital rubella after immunization has so far not been found. The theoretic risk of congenital complications after immunization is 2%, contrasted with a 30% or greater risk after maternal rubella infection in the first trimester [63]. However, because the rubella virus can cross the placenta, it is advised that women vaccinated against rubella avoid becoming pregnant for at least 3 months after the administration of vaccine [8,62]. The minimal risk to the fetus does not mandate automatic termination of a pregnancy following vaccination.

1. Fetal Effects

Congenital rubella can be quite devastating to the fetus, leading to death, low birth weight, deafness, congenital heart disease, and mental retardation. The specific effects on the fetus depend on the time of infection. The most vulnerable time period is during the first 2 months of gestation, when the fetus has a 65–90% chance of being affected (spontaneous abortion or congenital defects) [64]. During the third month of fetal life the chance of developing a single congenital defect decreases to about 30–35%. It is generally held that, for maternal illness occurring after the 20th week of gestation, the fetal damage is reduced to deafness occurring at 1–2% [65].

Whether reinfection with rubella that occurs during pregnancy can result in transmission has been debated for a long time.
Many of the case reports documenting high rates of fetal defects actually refer to primary maternal infections; in subclinical cases of reinfection the rate of fetal complications may be nonexistent [66].

B. Gender-Specific Manifestations

Complications of rubella are quite rare and include arthritis of the small joints of upper extremities and knees and seem to affect predominantly women. Rubella vaccination itself has also been found to be associated with joint complications, particularly in women. In 2001 an analysis of the Vaccine Adverse Events Reporting System database concluded that such an association was indeed observed following immunizations from 1991 to 1998 [67].

XV. Lymphocytic Choriomeningitis Virus

The lymphocytic choriomeningitis virus belongs to the arenaviruses family; its reservoir is the *Mus domesticus* and *Mus musculus*, the house mouse. LCMV infection in humans occurs only in Europe and the Americas with cases occurring most commonly in the autumn, during times of lower humidity. Infections among humans are associated with substandard, mouse-infested, inner-city dwellings and the cleaning of rodent-infested barns. Most infections occur among young adults. The mode of transmission is not clear, but it most likely involves aerosolized virions, direct contact with rodents, and rodent bites [68].

The initial signs and symptoms of LCMV infection include fever and headaches that come on insidiously, resolve for 2–4 days, only to return with increased intensity. During the second febrile episode patients may exhibit signs of meningitis with a predominantly lymphocytic CSF profile; encephalomyelitis may ensue with psychosis, paraplegia, and abnormalities in cranial and autonomic nervous system function. Other complications include orchitis, myocarditis, and arthritis. Diagnosis can be made with IgM ELISA of serum and CSF. Treatment of arenavirus infection is mostly supportive but may include administration of Ribavirin in very severe infections. Prevention of spread by household rodent control is crucial in limiting transmission of the disease.

A. Considerations Specific to Pregnancy

It has been shown that arenaviruses readily invade the fetus and can lead to fetal infection. The initial case report of intrauterine infection in the 1950s involved an infant who was born in England 12 days after maternal illness developed, became febrile and lethargic, and died at 12 days of age [69].

Additional studies from Germany, Lithuania, and France have documented the association of intrauterine LCMV infection with the occurrence of spontaneous abortion as well as with congenital hydrocephalus, microcephalus, and chorioretinitis in live-born infants [68].

These sequelae of fetal infection have only been recognized within the last decade in the United States. Since then there have been little more than 50 documented cases of congenital LCMV infection worldwide. Rodent exposure was noted in 18 out of 38 mothers of infected infants. The transplacental infection of the fetus presumably occurred during symptomatic maternal viremic illness, primarily during the first and second trimesters, and was documented in 21 out of 33. Mice infected in utero asymmetrically shed LCMV in their feces, urine, saliva, breast milk, and semen and transmit the infection to humans (and hamsters) by direct contact or inhalation. Therefore, pregnant women should be advised to avoid contact with these rodents and their secretions, as they are similarly counseled to avoid contact with cat litter to prevent congenital toxoplasmosis [68,70,71].

XVI. Suggestions for Further Investigations

- What is the biologic basis for gender-based differences in the response to viral infection?
- What can be done to protect pregnant women from serious viral infections?
- What is the future of herpesvirus vaccines, especially against those herpesviruses most likely to result in fetal damage? Can reactivation of latent infections be prevented?

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