Viral Infections During Pregnancy

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Viral infections during pregnancy have long been considered benign conditions with a few notable exceptions, such as herpes virus. The recent Ebola outbreak and other viral epidemics and pandemics show how pregnant women suffer worse outcomes (such as preterm labor and adverse fetal outcomes) than the general population and non-pregnant women. New knowledge about the ways the maternal–fetal interface and placenta interact with the maternal immune system may explain these findings. Once thought to be 'immunosuppressed', the pregnant woman actually undergoes an immunological transformation, where the immune system is necessary to promote and support the pregnancy and growing fetus. When this protection is breached, as in a viral infection, this security is weakened and infection with other microorganisms can then propagate and lead to outcomes, such as preterm labor. In this manuscript, we review the major viral infections relevant to pregnancy and offer potential mechanisms for the associated adverse pregnancy outcomes.

Introduction

Perinatal outcomes from viral infections during pregnancy can range from no effect to pregnancy loss by spontaneous abortion to fetal infection with resulting congenital viral syndromes. Prenatal care currently holds no true standard for antenatal management of viral infections during pregnancy, aside from those known as TORCH infections (toxoplasmosis, 'other', rubella, CMV, and HSV). And while these guidelines allow for a diagnosis of infection, no treatment or preventative strategy is available to prevent adverse pregnancy outcomes.

The importance of understanding the role of viral infection during pregnancy is becoming more relevant as we confront growing risks of pandemics, which may significantly affect the pregnant mother and the fetus.[1] There is strong epidemiologic evidence that pregnant women are at higher risk of severe illness and mortality from viral infections,[2,3] noticeably during pandemics such as influenza, EBOLA and Lassa fever.[4,5] Furthermore, viral infection may predispose the pregnancy to preterm labor and preterm delivery by infection with other superimposed microorganisms.[6–8] Consequently, understanding why pregnant women are at higher risk is vital to design the appropriate approaches for treatment as well as for prevention.

In this manuscript, we review the main viral infections reported associated with pregnancy and discuss potential mechanisms that explain why pregnant women are a high-risk population.

Herpes simplex virus

Genital herpes simplex virus (HSV-2) is the most common sexually transmitted infection among the adult female population of the United States. The Centers for Disease Control and Prevention (CDC) estimates that about one of six people overall (one of five women aged 14–49 and one of nine men aged 14–49) in the United States has genital HSV, with almost 800,000 new cases identified each year.[9]

HSV-1 (HSV-1) and 2 (HSV-2) are part of a large family of DNA viruses of which eight are known to be infectious in humans. HSV-1 and 2 are transmitted across epithelial mucosal cells as well as through skin interruptions and migrate to nerve tissues where they persist latent. HSV-1 predominates in orofacial lesions and typically is found in the trigeminal ganglia, while HSV-2 is most commonly found in the lumbosacral ganglia. Both HSV-1 and HSV-2 can cause genital lesions and shedding.

According to The National Health and Nutrition Examination Surveys (NHANES), there is an overall decrease in the seroprevalence of HSV-1 by 7% and of HSV-2 by 19%.[2] NHANES indicate that the rates of HSV-2 are higher among women (23.1%) than men (11.2%) in the general population. Factors that affect a woman's risk of infection before pregnancy include ethnicity, poverty, cocaine abuse, earlier onset of sexual activity, number of lifetime sexual partners, sexual behavior, and the presence of bacterial vaginosis.[10]

The overall seroprevalence of HSV among pregnant women is 72%.[11] This represents any exposure to either HSV-1 or HSV-2 that resulted in infection and antibody formation. During pregnancy, HSV infection has been associated with spontaneous abortion, intrauterine growth restriction, preterm labor, and congenital and neonatal herpes infections.[12] However, the clinical management revolves around decreasing vertical transmission to the fetus, thereby decreasing the risk of neonatal herpes infection.

The presence of antibodies to both HSV-1 and HSV-2 at the onset of pregnancy (prior seroconversion) has the least risk of perinatal transmission. In contrast, primary or first genital HSV infection late in pregnancy carries a 30–50% risk of neonatal infection, while early pregnancy infection carries a risk of <1%.[9,13] If primary HSV infection occurs during late pregnancy antibodies are not developed in time to suppress viral replication and shedding before labor. Transplacental or ascending transmembrane transmission of HSV from mother to fetus during pregnancy is uncommon; 80–90% of perinatal transmission occurs during labor and delivery.[14] However, neonatal infection with HSV can also occur in the setting of recurrent herpes. Symptom recurrence producing viral shedding at the onset of labor is associated with up to a 3% risk of neonatal herpes; both young age and recent infection are associated with increased viral shedding.[15,16] Interestingly, asymptomatic viral shedding in recurrent disease at term has not been associated with neonatal disease.[14]

Neonatal herpes infection is classified into three categories: localized skin, eye, and mouth (SEM); central nervous system (CNS) with or without SEM; and disseminated disease (which carries a mortality rate in excess of 80%, if untreated).[14,15,17,18] Infected newborns can exhibit significant neurologic deficits, blindness, seizures, and learning disabilities.

Suppressive antiviral therapy during the last month of pregnancy reduces the likelihood of asymptomatic viral shedding, clinical HSV recurrence, and cesarean delivery for recurrent lesions.[19–22] When lesions or prodromal symptoms are present at the onset of labor, cesarean section is recommended to minimize the risk of viral exposure to the infant, even if suppressive therapy has been used.[23]

Among women with asymptomatic HSV in labor, invasive procedures such as amniotomy, the use of fetal scalp electrodes,[24] and operative vaginal delivery,[25] should be avoided. This decreases fetal exposure to vaginal secretions potentially containing the virus. Active management should be considered in these women when membranes rupture before the onset of labor.

When there is preterm premature rupture of the membranes (PPROM), the risks of prematurity must be weighed against the risks of HSV transmission. Each case will be dependent on the gestational age and clinical picture. There is no consensus on the best timing of delivery for women with PPROM and a history of HSV.

Varicella zoster virus

Varicella, also known as chickenpox, is the acute primary disease of varicella zoster virus. It is a common, highly contagious, self-limiting disease seen mainly during childhood. It is transmitted by respiratory droplets or close contact and causes a widespread maculopapular to vesicular rash that starts on the face and trunk and then moves to the extremities. The virus incubates for 15 days and is communicable 2 days before the onset of the rash until all the lesions have crusted or disappear.[26] After an initial episode with varicella zoster leading to chickenpox, the virus may persist latent in the dorsal root ganglia for years. Reactivation results in herpes zoster, which is more common in adults.

The incidence of varicella in pregnancy is 0.7 of 1000. Because varicella is mainly a disease of

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childhood in the United States, most women are immune before they become pregnant.[27] However, primary varicella infection during pregnancy is associated with significant maternal and fetal morbidity and mortality. While the childhood illness is self-limiting and mild, if varicella pneumonia develops during pregnancy, it can run a more fulminant course. Approximately 10–20% of pregnant women who are infected with varicella will develop pneumonia, which carries a mortality rate of up to 40%.[9]

Fetal morbidity and mortality is related to the development of congenital varicella syndrome. This syndrome is characterized by limb hypoplasia, microcephaly, hydrocephaly, cataracts, intrauterine growth restriction, and mental retardation.[28] The risk of congenital varicella syndrome ranges from 0.4 to 2% with maternal varicella infection during the first 20 weeks of gestation.[28–31] Development of this syndrome is thought to be a result of reactivation of the varicella virus *in utero*, as opposed to primary infection of the fetus.[30,32,33]

Herpes zoster in pregnancy is much less common than varicella, occurring in 1/10,000 pregnancies, or 0.1%.[26] The risk of the congenital varicella syndrome is negligible, because antibodies in the maternal blood prevent the virus from crossing the placenta and infecting the fetus. In 1994, Enders and colleagues showed no clinical evidence of infection in infants born to 366 women with herpes zoster in pregnancy.[29]

Neonatal infection may occur in 10–20% of neonates whose mothers became acutely infected from 5 days before delivery to 2 days after the delivery. It results from hematogenous dissemination of the virus across the placenta in the absence of maternal antibodies. Infants become symptomatic 5–10 days postpartum. The clinical picture may vary from skin lesions to systemic illness, which has a mortality rate of about 30%.[33–37]

Treatment for the pregnant woman primarily targets decreasing maternal morbidity, as no treatment regimen has shown a decrease in the incidence of vertical transmission.

Cytomegalovirus

Cytomegalovirus (CMV) is a ubiquitous virus with variable clinical manifestations. Seroprevalence increases with age and differs based on geographic area and socioeconomic status. CMV infects 60% of women of childbearing age in developed countries and 90% in developing countries.[38] The resulting sero-positivity (maternal antibody status to CMV) is the most important factor in combatting congenital CMV infection. The remaining 40% of women in developed countries (such as the United States) are susceptible to infection; and if this infection occurs during pregnancy, it can have detrimental effects on the pregnancy.

Person-to-person transmission occurs by contact with infected nasopharyngeal secretions, urine, saliva, semen, cervical and vaginal secretions, breast milk, tissue, or blood. Primary maternal infection occurs in 1–4% of susceptible women, and reactivation may occur in approximately 10% of sero-positive women. Maternal infection with CMV during the antepartum period goes undetected the majority of the time, but can manifest as a mild febrile illness with non-specific symptoms such as fatigue, myalgias, rhinitis, pharyngitis, and headache. Furthermore, pregnancy does not appear to affect the clinical severity of the infection.

Vertical transmission (from the mother to the fetus or newborn) occurs most commonly after maternal primary infection, usually by the following mechanisms: transplacental after the virus infects the placenta, intrapartum via ingestion or aspiration of cervicovaginal secretions during delivery, postpartum via breastfeeding, and ascending from the maternal genital tract antepartum (rare).

In terms of fetal effects of maternal infection, CMV is the most common congenital viral infection, with a birth prevalence of about 0.5% (range 0.2–2.5%).[39,40] CMV primarily affects the ventricle, the organ of Corti and the neurons of the eighth cranial nerve, which explains why it is the leading cause of congenital hearing loss. Furthermore, human neuronal cells are able to be infected *in-vitro* with CMV, which may explain the central nervous system effects during fetal development.[41]

The rate of fetal transmission appears to increase with advancing gestation. A review that pooled data from nine studies of maternal–fetal CMV transmission reported first, second, and third trimester transmission rates of 36.5, 40.1, and 65%, respectively.[42,43] However, while the rate of transmission correlates with advancing gestation, the severity of the disease is inversely related to gestational age.

Most newborns of women with primary CMV infection and almost all newborns of women with non-primary infection in pregnancy are initially asymptomatic. Ten to 15% of these initially

asymptomatic newborns develop neurodevelopmental damage within the first 3 years of life.[44,45] Approximately 5–20% of newborns of mothers with primary CMV infection will have symptoms at birth. The mortality rate of these newborns is about 5%. Five to 15% of the asymptomatic newborns will develop sequelae later in life.[46–48]

Prenatal diagnosis of fetal CMV is based on amniocentesis performed 6 weeks after the presumed time of infection and after 21 weeks of gestation. While sonographic findings often imply a poor prognosis, their absence does not guarantee a normal outcome. The value of quantitative determination of CMV DNA in the amniotic fluid and the effectiveness of prenatal therapy has not been proven.[41] Given this fact and the ubiquitous nature of the virus, universal screening for pregnant women is currently not recommended.

Rubella

The name rubella is derived from Latin, meaning 'little red', because it was initially thought to be a variant of measles or scarlet fever. However, in the mid-1800s, a German physician distinguished rubella as a distinct clinical entity, hence it being commonly known as German measles. The rubella virus, an enveloped RNA virus, is classified as a togavirus. It is transmitted through respiratory droplets and is primarily a mild disease in children. In adults, rubella is a self-limited disease characterized by rash. The rash characteristically begins on the face and spreads to the trunk and extremities. The incubation period is 12–23 days. The infectious period is from 7 days before to 7 days after rash onset.[49] Importantly, rubella can be asymptomatic in 25–50% of the cases. When maternal infection occurs in the first trimester, fetal infection rates are up to 50%, dropping to <1% after 12 weeks. (Peripartum maternal infection does not seem to increase the risk of CRS.) Diagnosis of primary maternal infection should be made by serologic tests. Diagnosis of fetal infection includes detection of fetal serum IgM (but not until after 22–24 weeks of gestation) or viral culture of the amniotic fluid.

Pregnancy outcomes as a result of maternal rubella infection include spontaneous abortion, fetal infection, stillbirths or fetal growth restriction, and the congenital rubella syndrome (CRS). The CRS represents the neonatal manifestations of antenatal infection with the rubella virus. The risk of CRS varies according to the gestational age at which maternal infection occurs.[50] Therefore, counseling regarding the fetal risk and management must be individualized. Two proposed mechanisms for rubella cytopathology include virus-induced inhibition of cell division[51] and direct cytopathic effects.[50]

Fortunately, however, since the development of the rubella vaccine in the 1960s, along with the implementation of universal screening and vaccination pre-pregnancy and postpartum for childbearing women, the incidence of congenital rubella infection has decreased substantially in the United States.[40] Even so, not all pregnant women are immune to rubella. Certain populations are not immunized because they are missed, refuse immunization, or come from countries where rubella vaccination is not part of the routine immunization program.[9,52]

HIV

According to the Centers for Disease Control and Prevention (CDC), about 50,000 people get infected with HIV each year in the United States. In 2010, of the 1.1 million people in the United States living with HIV, 47,500 people had new HIV infections and one in four people were women.[52] About 80% of new cases in women in the United States are contracted through heterosexual intercourse, 20% by contaminated needles and the remaining cases through blood transfusions (no longer occurring as transmission factor due to universal screening of blood products for HIV) and maternal-child transmission. In the United States, African American and Hispanic women represent 25% of the female population but 82% of the total number of women with AIDS. Furthermore, black women alone account for 80% of newly diagnosed HIV/AIDS cases.[28]

Eventually, most people infected with HIV develop AIDS and die from opportunistic disease or malignancy. Without treatment, 90% of people with HIV progress to AIDS after 10–15 years. Treatment with antiretroviral medication prolongs life expectancy even after progression to AIDS such that the average survival with antiretroviral treatment exceeds 15 years.[53,54]

The most common clinical manifestations of the acute retroviral syndrome include fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache. Diagnosis is made with HIV immunoassay (ELISA or Western blot) and HIV viral RNA detection. If left untreated levels of CD4 T cells decline

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and opportunistic infections lead to death. However, as described above, with antiretroviral treatment, life expectancy has increased significantly.

The reduction in mother-to-child transmission of human immunodeficiency virus (HIV) is regarded as one of the most effective public health initiatives in the United States. While pregnancy does not affect disease course, HIV infection in pregnancy includes a risk of vertical transmission. The exact mechanism of mother-to-child transmission of HIV remains unknown at this time. This transmission may occur during intrauterine life, delivery, or breastfeeding. The greatest risk of transmission is attributed to advanced maternal disease, likely due to a high maternal HIV viral load. With no treatment, the risk of vertical transmission is as high as 25%, but with the implementation of universal antenatal HIV testing, counseling, maternal antiretroviral medication, and neonatal post-exposure prophylaxis for newborns of women with HIV, delivery by cesarean section prior to onset of labor, and discouraging breastfeeding, the mother-to-infant transmission has decreased to <1% in the United States.[52]

The hormonal status, the regulation of the mucosal environment in the female reproductive tract, and the morphological changes in the female reproductive tract associated with pregnancy play a critical role in the susceptibility to HIV. This is an area that we have only begun to understand and involves multiple complex biological and clinical factors that need to be carefully evaluated.[55] Several reviews on the subject have been recently published where these aspects are further elaborated.[56–59]

Hepatitis

Acute viral hepatitis is the most common cause of jaundice in pregnancy. The course of most viral infections is not affected by pregnancy.

Hepatitis A

Hepatitis A virus (HAV) infection is the second most common form of viral hepatitis in the United States. It is an RNA virus that is transmitted by the fecal–oral route.[60–62] Infections occur early in life in areas where sanitation is poor, and living conditions are crowded.[63] The incidence of acute HAV infection in pregnancy is approximately 1:1000 women. Vertical transmission of HAV during the pregnancy or puerperium is rare.[64–68] Pregnancy should not impact a physician's management of HAV infection or vice versa.

Hepatitis B

Hepatitis B virus (HBV) is the most common form of chronic hepatitis around the world. Chronic carriers can continue to transmit the disease for many years before becoming symptomatic.[69] Infection occurs very often in early childhood when it is asymptomatic and then leads to the chronic carrier state. Chronic HBV infection leads to increased risk for chronic hepatic insufficiency, cirrhosis, and hepatocellular carcinoma.

In the United States, the incidence of HBV infection has declined from 8.5 cases to 1.5 cases per 100,000 from 1990 to 2007. Approximately 0.5% of the US population is HbsAg positive, and 5% is anti-HBc positive.[70]

The age group most likely to be affected worldwide is the newborn population, particularly in areas with high prevalence of disease and lack of diagnosis of infected women whose infants are at risk of becoming chronic carriers. On the other hand, the primary causes of transmission in the young adult population where perinatal screening and adequate newborn prophylaxis exist are the exposure to contaminated blood products, body fluids, or sexual contact.

Acute HBV infection during pregnancy usually is mild and not associated with teratogenicity or mortality. Treatment is mainly supportive, with monitoring of liver biochemical tests and prothrombin time. Unless the patient has acute liver failure or protracted severe hepatitis, antiviral therapy is usually unnecessary. Chronic HBV infection is generally well tolerated in women who do not have advanced liver disease. But, because these patients occasionally will develop a hepatitis flare, liver biochemical tests should be monitored every trimester and postpartum.

A high maternal viral load appears to be the most important risk factor for perinatal transmission. Transplacental transmission and transmission due to obstetrical procedures are less frequent causes, while breastfeeding does not appear to pose a substantial risk. Delivery decisions should be made in the context of the usual obstetric indications.

Management options are available to decrease the risk of perinatal transmission. Universal screening of all pregnant women allows for identification of Hepatitis B surface antigen positive women. Women found to be positive should also be screened for HIV

and other forms of hepatitis such as hepatitis A and hepatitis C. Monitoring of liver biochemical tests and viral load help guide management and extent of disease. All infants of mothers with HBV should receive passive-active immunization with hepatitis B IgG and the hepatitis B vaccine within 12 hr of delivery.

Hepatitis C

The hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma around the world.[71] HCV infection has a slow onset with symptoms in about 25% of patients.[59] Approximately 40% of patients infected with HCV recover completely and the rest become chronic carriers. Twenty percent of the carriers develop cirrhosis and of those, up to 20% develop liver cancer.[70]

HCV-related end stage liver disease is the most common chronic blood borne infection and the leading reason for liver transplantation in the United States. New HCV infections have decreased by more than 80% since 1990.[72] There are an estimated 4 million cases of chronic liver disease and 2.7–3.4 million cases of HCV infection.[73,74] There are 25,000–38,000 new cases of HCV diagnosed every year with a prevalence of 1.6%.[73,75] Of the newly diagnosed cases, only 6300 (17%) are symptomatic.[76]

Acute HCV infection leads to symptomatic hepatitis in fewer than 20% of patients; 15% of acute liver disease in the United States is due to HCV.[77] The peak age of incidence of acute HCV is between 20 and 39 years.[78] In the pregnant population, the prevalence of HCV is estimated to be <1–5% with the highest prevalence in the African American population (6.1%) and the lowest in the Latin population (2.8%).[79,80] Approximately 75% of asymptomatic patients are chronically infected. They are a source of transmission to others and are at risk for chronic liver disease or other HCV-related chronic diseases.

Approximately 60% of all new infections occur via intravenous (IV) drug use,[80] 10–20% by sexual transmission,[81] <6% by blood transfusion, and the remainder includes occupational and unknown exposures.[82] Only 25% of pregnant women report receiving blood products or IV drug use when HCV infection is diagnosed.[83] Concurrent alcoholism, IV drug use (38%), and coexisting HIV infection (33%) are important associated risk factors.[82,84] The decline observed in the incidence and prevalence of HCV is attributed to needle exchange programs among intravenous drug users and improved blood donor screening. This has led to a relative increase in the importance of accidental needle sticks, and sexual and perinatal transmission in the incidence of HCV infections.[71]

The World Health Organization (WHO) estimates that about 3% of the world's population has been infected with HCV and that there are more than 170 million chronic carriers who are at risk of developing liver cirrhosis and/or liver cancer.[85] The highest prevalence is in Egypt (18–22%) and the lowest in Sweden (0.003%).[71,85] As many as 2–4 million persons may be chronically infected in the United States, 5–10 million in Europe and about 12 million in India. Of these, about 25% are symptomatic, but 60–80% may progress to chronic liver disease and 20% of these develop cirrhosis.[85]

Women chronically infected with hepatitis C may have uneventful pregnancies; although vertical transmission is the greatest concern. In the United States and other industrialized nations, because of vaccination programs against hepatitis B, hepatitis C virus (HCV) has become the primary cause of chronic viral hepatitis in children, with vertical transmission becoming the leading source of infection.[86–88] The mechanism underlying vertical transmission is poorly understood. Overall the transmission rate appears to be <2%, when adjusted for certain clinical variables. For example, HIV coinfection results in a 19% transmission rate.[89,90] During pregnancy, pregnant women should be seen regularly by a gastroenterologist to monitor liver biochemical tests and viral load. During labor, prolonged rupture of membranes should be avoided, as well as invasive obstetric procedures.[91] Cesarean delivery should be reserved for the usual obstetric indications. Breastfeeding is not contraindicated.

Hepatitis E

Hepatitis E is caused by the hepatitis E virus (HEV). Although initially thought to be hepatitis A, most waterborne epidemics of hepatitis in developing countries are known to be due to hepatitis E. It is rare and sporadic in industrialized countries.[92] It is usually passed by fecal–oral transmission through a contaminated water supply.[93] The infection is typically mild and self-limited without chronicity or clinical sequelae.

During pregnancy, the risk of fulminant disease and maternal mortality occurs in 20% of patients

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when disease presents during the third trimester. Premature deliveries with high infant mortality of up to 33% are also observed.[94] Although the mechanism underlying the increased mortality is unknown, the reported complications include gestational hypertension, preeclampsia, proteinuria, edema, and kidney disease. One possible mechanism of disease could be a direct or indirect effect on the kidneys, which may precipitate disease and increase maternal mortality.[95]

Influenza

Symptoms of influenza include cough, fever, malaise, rhinitis, myalgias, headache, chills, and sore throat. Less common symptoms include nausea and vomiting, otitis, and conjunctival burning. Signs of influenza include fever, tachycardia, facial flushing, clear nasal discharge, and cervical adenopathy.

Pregnant women are at high risk for severe complications of influenza during seasonal influenza periods[96] and pandemics.[97–100] In addition, some studies suggest an increased risk for adverse outcomes among infants born to mothers infected with influenza during pregnancy.[101–104]

Influenza viruses that infect humans are classified into three principal types (A, B, and C), of which types A and B are important causes of human disease. Types A and B are associated with seasonal epidemics; only type A viruses have caused pandemics. Influenza A viruses are further classified on the basis of two surface proteins, haemagglutinin (H) and neuraminidase (N). H1N1 designates a specific subtype of influenza A. Minor mutations that result in subtle changes in these proteins (antigenic drift) occur continuously. Because these mutations produce viruses that can be sufficiently different antigenically from previous influenza viruses, influenza vaccines must be updated annually. More dramatic changes in the surface proteins of influenza viruses, through mutation of non-human (e.g., avian or swine) viruses or reassortment of human and non-human viruses, result in the creation of novel human subtypes (termed antigenic shift). When novel subtypes that can be efficiently transmitted among humans target certain populations, a pandemic of influenza can occur.[105]

Pregnancy has been the highest risk factor for increased illness and death for both pandemic and seasonal influenza.[2] Although appropriate non-pregnant control groups were generally not available, mortality rates among pregnant women in the pandemics of 1918 and 1957 appeared to be abnormally high.[97,99] Among 1350 reported cases of influenza among pregnant women during the pandemic of 1918, the proportion of deaths was reported to be 27%.[97] Similarly, among a small case series of 86 pregnant women hospitalized in Chicago for influenza in 1918, 45% died.[97] Among pregnancy-associated deaths in Minnesota during the 1957 pandemic, influenza was the leading cause of death, accounting for nearly 20% of deaths associated with pregnancy during the pandemic period; half of women of reproductive age who died were pregnant.[99]

Pregnant women have also been shown to be at increased risk for influenza complications during seasonal influenza periods.[102] In a large study of >4300 women of reproductive age during 19 influenza seasons, pregnant women were compared with postpartum women (a group considered to be most similar to pregnant women demographically and with regard to their health) and were found to be significantly more likely to be hospitalized for a cardiopulmonary event during the influenza season.[96] The risk for hospitalization increased as pregnancy progressed, with women at term nearly five times more likely to be hospitalized than postpartum women.[96] Similarly, during three influenza seasons in the late 1970s, rates of medical visits for acute respiratory disease were more than twice as high among pregnant women than non-pregnant women.[106] At particularly high risk during the influenza season are pregnant women with underlying medical conditions for which influenza vaccination is recommended, such as asthma.[107] On the basis of these data, pregnant women are considered a population for which special considerations for prevention and treatment for influenza have been made.

Although certain infections are well recognized to increase the risk for adverse pregnancy outcomes, the effects of maternal influenza infection on the fetus are not well understood. Viremia is believed to occur infrequently in influenza,[108] and placental transmission of the virus also appears to be rare.[109] However, even in the absence of fetal viral infection, murine models suggest that adverse effects can still occur. Prenatal influenza infection in the mouse has been associated with histopathologic changes in the brain[110] and behavioral alterations[111] in offspring. Although influenza virus RNA has not been detected in the fetal brain, these changes suggest that fetal effects could be secondary to the maternal

inflammatory response, rather than the result of a direct viral effect.[112]

Adverse pregnancy outcomes have been reported following previous influenza pandemics. During the influenza pandemic of 1918, remarkably high rates of spontaneous abortion and preterm birth were reported,[97,98] especially among women with pneumonia (for example, in one study, >50% of pregnancies in which the pregnant woman had influenza and accompanying pneumonia were not carried successfully to term).[97] During the Asian influenza pandemic of 1957, studies suggested a possible increase in defects of the central nervous system[102–104] and several other adverse outcomes, including birth defects, spontaneous pregnancy loss,[104] fetal death, and preterm delivery.[100] Studies of the effects of seasonal influenza infection on the fetus have been contradictory. A small increased risk for birth defects in general and for specific birth defects have been observed in some but not all studies.[101] Using data from a recent case–control study, investigators showed that mothers of infants with any type of birth defect were slightly more likely to report influenza during early pregnancy than mothers of control infants (adjusted odds ratio 1.4; 95% confidence intervals 1.3–1.6), with statistically significant associations for cleft lip with or without cleft palate, and neural tube and congenital heart defects. Verification of maternal report of influenza illness with prospectively collected clinical data was possible for similar numbers of case and control infants,[101] which suggests that recall bias was unlikely to explain the association. The risk associated with influenza was reduced for women who received treatment with antipyretic medications and for those who had taken folic acid before and during early pregnancy.[101]

Associations between maternal influenza infection after both pandemic and seasonal influenza and outcomes observed long after birth have been reported. Associations between maternal influenza infection and childhood leukemia,[113] schizophrenia,[114] and Parkinson's disease[115] have been suggested by some studies. Even if the influenza virus does not have a direct effect on the fetus, fever that often accompanies influenza infection could have adverse effects. Both animal and human epidemiologic studies suggest that hyperthermia is associated with an increased risk for adverse outcomes,[116] especially neural tube defects.[117] Factors that might attenuate this risk include shorter fever duration,[118] use of fever-reducing medications,[118–120] and use of folic acid-containing supplements.[119] However, there is evidence that vaccination works and is protective for both mother and fetus, especially for high-risk subpopulations, such as immunosuppressed pregnant women. A recent study in South Africa showed that IIV3 vaccination in pregnant HIV-uninfected and HIV-infected women was immunogenic and provided protection against confirmed influenza.[121]

CDC Recommendations: The CDC currently recommends influenza vaccine for all pregnant women in any trimester during flu season. Furthermore, pregnant women with symptoms of influenza should be screened and treated immediately, especially those with comorbid medical conditions.

Ebola and Lassa fever

Ebola and Lassa viruses cause hemorrhagic fevers that have been reported mainly in Africa.[122] However, as a result of the most recent Ebola epidemic with infected individuals traveling outside of Africa, these types of viral infections became a global challenge, especially due to the potential effect in pregnancy and the newborn.

Ebola virus disease is a rare but severe viral hemorrhagic fever that is caused by five different species of Ebola virus. The major outbreaks of Ebola Hemorrhagic fever (EHF) occurred in Africa, especially in resource-constrained regions. The virus species (Zaire ebolavirus) causing the current epidemic was identified in 1976 in Kikwit, the Democratic Republic of the Congo. During that epidemic, the numbers of infected women were higher than men, although largely due to cultural practices rather than biological differences.[5,123,124]

During previous epidemics, mortality among pregnant women was found to be higher than in the general population or non-pregnant women. In the 1976 epidemic, 46% of the 177 Ebola-infected women were pregnant and the overall mortality among pregnant women was 89%. A major clinical manifestation was vaginal and uterine bleeding with 93% mortality within 10 days of illness onset.[125,126] Moreover, a significant increase in preterm birth and abortion has been reported in the different epidemics.[5,127] Twenty three percent of infected pregnant women had spontaneous abortions in the 1976 epidemic; while 67% of pregnancies were reported to end with abortion in the 1995 epidemic.[125,126,128]

Lassa fever or Lassa hemorrhagic fever (LHF) is an acute viral hemorrhagic fever caused by the Lassa

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virus and was first described in 1969 in the town of Lassa in Nigeria.[122,129,130] Lassa fever is endemic in eastern Sierra Leone where it is a major cause of mortality, especially in pregnant women.[131] Interestingly, the condition of the mother improved rapidly after evacuation of the uterus whether by spontaneous abortion or normal delivery.[4] Ten of 26 women without delivery died, while only four of 39 women that delivered died.[4]

Viral infection and pregnancy: old and new concepts

One of the main hypotheses used to explain the increased risk for infection and mortality during pregnancy has been the concept of 'pregnancy as an immune-suppressed condition'.[132] The 'paradox of pregnancy' as a semi-allograft has been approached from the point of perspective of organ transplantation. The view of the fetus as an organ transplant, and the requirement of systemic immune suppression for the success of the transplant, led to the proposal of pregnancy as a condition of systemic immune suppression as a requirement for the success of the pregnancy. From this point of view, similarly as in immune-suppressed patients, pregnancy is in a state of weak immunologic protection.

This concept has been tested for many years in animal models as well as in patients with fertility problems. Unfortunately, after almost 50 years of research following this assumption, there is a lack of evidence to support this hypothesis.

Therefore, it is important to evaluate the immunologic aspects associated with pregnancy in order to further understand the potential biological reasons associated with the risk of infection during pregnancy. One wonders why the model of transplantation may not represent the correct immunological situation of pregnancy: During transplantation, there is a major influx of foreign antigens as a result of the introduction of a fully foreign organ. Under this circumstance, the host immune system acutely reacts to the foreign antigens and mounts an immunologic response to reject the source of foreign antigens. During pregnancy, the process is different. Pregnancy is a slow and gradual process where paternal/fetal antigens are released in a gradual and increasing manner as the blastocyst grows into an embryo and then into a fetus. The exposure of small amounts of foreign antigens during this process may actually induce *tolerance* rather than rejection. Consequently, pregnancy, contrary to transplantation, does not require systemic immune suppression.

A second aspect that has been ignored for many years is the role of the placenta. Pregnant women represent an immunologically unique population because their immune system is influenced by signals originating from the placenta.[7,133] The presence of the fetus and placenta alters maternal immunity and physiology to sustain and protect the pregnancy. We and others have shown that the placenta may function as an immune modulatory organ that regulates the immune responses of cells present both at the implantation site as well as systemically.[134–136] However, this modulation is not suppressive, but protective. In general, the maternal immune system is well prepared to control infections and ensure the survival of the fetus. Paradoxically, the placenta is also a target for viral infections. Recent studies suggest that although the placenta can be infected by viruses, it has a unique capacity to prevent expansion of the virus and transmission to the fetus.[8,133,137,138] What is not clear is the effect of a viral infection on the normal homeostasis of the placenta and its interaction with the maternal immune system. As discussed below in more detail, a viral infection of the placenta might affect the normal homeostasis at the implantation site, as well as the systemic immune system of the mother, which will determine the type of immune response that is elicited in the presence of normal or abnormal microorganisms.

Pregnancy complications are the result of polymicrobial infections

Preterm delivery, defined as delivery prior to 37 completed weeks of gestation, is one of the most frequent obstetrical complications, occurring in 12% of all deliveries in the United States.[139–141] It is the leading cause of neonatal morbidity and a major cause of neonatal mortality. Premature infants suffer chronic long-term health issues and even severe neurological impairment if they survive. Maternal consequences range from cesarean delivery, labeling of 'high risk' in subsequent pregnancies with the need for intense surveillance with subsequent anxiety, and the stress of life-long care for a child. In addition, the healthcare costs of caring for these preterm infants after delivery likely exceeds $26 billion dollars a year.[108,142,143] While this complication of pregnancy has major medical, social, and economic

consequences, the cause of spontaneous preterm birth is unknown.

It has been well established that adverse pregnancy outcomes have been linked to bacterial infections, such as chorioamnionitis and pyelonephritis.[39,144–147] On the contrary, viral infections have long been considered benign, with a few exceptions, some of which are listed above. For example, in the clinical setting, a pregnant woman with a cold or viral upper respiratory infection is treated symptomatically, and usually there is no concern for the pregnancy.[148] To be fair, the reasons for this stem from our lack of evidence of the adverse pregnancy outcomes that can occur as a result of these infections and the lack of effective measures to prevent these outcomes. Nevertheless, the sequelae of a viral infection can still lead to opportunistic infections that then can adversely affect the pregnancy. We investigated this novel approach to the problem of preterm labor and delivery: a polymicrobial etiology. This model illustrates how a viral infection during pregnancy, leads to an accentuated response to a low dose of bacterial product, leading to preterm labor and delivery.[133,136]

Our knowledge of the normal flora in the female reproductive tract and placenta has expanded in recent years. New technologies and methodologies have allowed us to further characterize the microorganisms in these two locations.[149–151] We see how commensal bacteria in the female reproductive tract can have relevant effects on the local immune function.[152,153] Furthermore, it has now become apparent that multiple different bacteria and viruses reside in the placenta and amniotic fluid, locations once thought to be sterile.[1,154,155] However, bacterial infection has been associated with a major cause of preterm labor.[156] But when do bacteria become a risk for the success of pregnancy? Our laboratory has recently examined the role of infection in the pathophysiology of preterm delivery. In contrast to multiple studies that have looked at single organisms as the lone etiology of premature labor and delivery, we investigated a different approach. Using a murine model of viral infection of the placenta, we characterized the subsequent response to bacteria. The viral infection was simulated using a murine herpes virus, MHV-68.[136,157] This virus is homologous to 2 human herpes viruses: Epstein–Barr virus and human herpes virus 8 (Kaposi's sarcoma-associated virus).[158] C57BL/6 pregnant mice were separated into four groups. The first group (the control group) was injected with DMEM media (vehicle) on day E8.5, then PBS on day E15.5. The second group was injected with DMEM on day E8.5, then 20 μg/kg of LPS on day E15.5. The third group was injected with 1×10^6 plaque-forming units of MHV-68 on day E8.5, then, PBS on day E15.5. The last group was injected with MHV on day E8.5, then LPS on day E15.5. The mice in the control and MHV-only group were unaffected and delivered normal-sized, term pups. The LPS only group had a preterm delivery rate of 29%, while the group injected with MHV then LPS all delivered preterm within 24 hr after LPS injection. Furthermore, significant inflammatory responses were noted in the placenta and decidua of the MHV with LPS group (group 4).

In addition to preterm delivery, the group that was injected with both MHV and LPS also had adverse fetal outcomes. Parallel experiments were performed where the mice were divided into the four groups and injected as above, then were sacrifice prior to delivery to examine the gestational sacs. The gestational sacs of the control, LPS-alone, and MHV-alone groups showed no visible effect. However, the sacs with the MHV and LPS treatment together showed marked necrosis and anomalies in the gestational sacs. Furthermore, all these fetuses demonstrated anatomical abnormalities, such as hydrocephalus and pulmonary and pericardial hemorrhage.[133]

Interestingly, no virus was detected in the fetuses of MHV-infected moms, as determined using a limited dilution plaque assay and confirmed by PCR. In contrast, isolated mouse embryonic fibroblast cells were able to be infected *in-vitro* with MHV-68, which suggests that the placenta provides immunologic protection to the fetus from viral infection during pregnancy.[159] However, even though no viral titers were detected in the fetuses, evidence of a fetal inflammatory response was noted as shown by elevated levels of IL-1, MCP-1, MIP1-β, IFN-γ, and TNF-α. The inflammatory response of the fetus may explain a developmental pathway of the observed anatomic changes. Moreover, the response of the fetal-placental unit during pregnancy can have far-reaching consequences, leading to postnatal developmental adverse outcomes, such as schizophrenia and psychosis.[112,160,161] Based on these findings, we propose that a viral infection of the placenta (the first hit) may affect the normal interaction with the local bacteria (the second hit), leading to a pro-inflammatory "cytokine storm" that leads to preterm birth.[133]

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Consequently, infection leading to preterm birth is a polymicrobial condition.

This new emerging data sheds light on an area of pregnancy once thought to be pure and pristine: the maternal–fetal interface and the placenta. In addition, immune effects of interactions between microorganisms can lead to significant perinatal outcomes, such as preterm delivery. Armed with the new information of the microbial environment and possible adverse pregnancy outcomes that can be associated with viruses and bacteria, new strategies are necessary to detect these microorganisms, even in asymptomatic pregnant women. By understanding this polymicrobial mechanism of disease, we can develop management and prevention strategies to decrease the incidence of preterm birth. Identifying the 'first hit' in the cascade can allow opportunities for intervention and possible prevention of premature labor and delivery. Only then will this devastating obstetrical problem be controlled and neonatal outcomes improved.

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