Infections in Pregnancy With COVID-19 and Other Respiratory RNA Virus Diseases Are Rarely, If Ever, Transmitted to the Fetus

Experiences With Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza

David A. Schwartz, MD, MS Hyg; Amareen Dhaliwal, BS

• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent of coronavirus disease 2019 (COVID-19), is similar to 2 other coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), in causing life-threatening maternal respiratory infections and systemic complications. Because of global concern for potential intrauterine transmission of SARS-CoV-2 from pregnant women to their infants, this report analyzes the effects on pregnancy of infections caused by SARS-CoV-2 and other respiratory RNA viruses, and examines the frequency of maternal-fetal transmission with SARS-CoV-2, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), influenza, respiratory syncytial virus (RSV), parainfluenza (HPIV), and metapneumovirus (hMPV). There have been no confirmed cases of intrauterine transmission reported with SARS-CoV-2 or any other coronaviruses—SARS and MERS. Influenza virus, despite causing approximately 1 billion annual infections globally, has only a few cases of confirmed or suspected intrauterine fetal infections reported. Respiratory syncytial virus is an unusual cause of illness among pregnant women, and with the exception of 1 premature infant with congenital pneumonia, no other cases of maternal-fetal infection are described. Parainfluenza virus and hMPV can produce symptomatic maternal infections but do not cause intrauterine fetal infection. In summary, it appears that the absence thus far of maternal-fetal transmission of the SARS-CoV-2 virus during the COVID-19 pandemic is similar to other coronaviruses, and is also consistent with the extreme rarity of suggested or confirmed cases of intrauterine transmission of other respiratory RNA viruses. This observation has important consequences for pregnant women because it appears that if intrauterine transmission of SARS-CoV-2 does eventually occur, it will be a rare event. Potential mechanisms of fetal protection from maternal viral infections are also discussed.

(*Arch Pathol Lab Med*. 2020;144:920–928; doi: 10.5858/arpa.2020-0211-SA)

One of the most serious consequences of infectious diseases is their potential to be transmitted from pregnant women to their unborn fetuses. The occurrence of this process—intrauterine vertical transmission—has been known for many decades to occur with specific microbial pathogens. In 1971 a group of investigators in Atlanta, Georgia, led by André Nahmias, MD,[1] developed an acronym to identify 4 of the most frequent causes of vertically transmitted infections that were recognized at that time.[2] This acronym—TORCH—represented ***T****oxoplasma*, **O**ther, **R**ubella virus, **C**ytomegalovirus, and the 2 **H**erpes simplex viruses (type 1 and type 2)—this group has been expanded subsequently to include syphilis, listeriosis, parvovirus, coxsackie virus, *Trypanosoma cruzi*, and others.[2] Since that time, vertical transmission from pregnant women to their fetuses has been a major problem with emergent viral diseases, such as the human immunodeficiency virus (HIV),[3,4] Ebola virus,[5–7] and, most recently, Zika virus.[8–10] These emerging viral diseases have resulted in major epidemics; caused significant perinatal morbidity and mortality, including maternal, fetal, and neonatal death; and continue to be significant public health problems for pregnant women and their infants. The 2 most important mechanisms for transmission of microbial agents from mother to infant include maternal hematogenous infection and ascending infection.[11] Most TORCH agents (with the notable exception of herpes simplex viruses) and emerging viral diseases are transmitted to the fetus via the maternal hematogenous route via the maternal-fetal interface—organisms circulating in the maternal bloodstream during pregnancy enter the placenta from uterine arteries, circulate in the intervillous space, and can pass to the fetus through

Accepted for publication April 24, 2020.
Published online April 27, 2020.
From the Department of Pathology, Medical College of Georgia, Augusta University, Augusta (Dr Schwartz); and the Boston University School of Medicine, Boston, Massachusetts (Ms Dhaliwal).
The authors have no relevant financial interest in the products or companies described in this article.
Corresponding author: David A. Schwartz, MD, MS Hyg, Department of Pathology, Medical College of Georgia, 1950 Grace Arbor Court, Atlanta, GA 30329 (email: davidalanschwartz@gmail.com).

Respiratory RNA Viruses and Maternal-Fetal Transmission				
Respiratory RNA Virus	**Prevalence**	**No. of Infected Pregnant Women Reported**	**Intrauterine Maternal-Fetal Transmission**	**Perinatal Deaths**
Severe acute respiratory syndrome coronavirus	8422 total cases globally	Approximately 37 cases reported[14] Estimates of up to 100 cases[17]	None	Yes[14,17]
Middle East respiratory syndrome coronavirus	2494 total cases globally	11 cases reported[14]	None	Yes[14,17]
Severe acute respiratory syndrome coronavirus 2	2 160 207 total cases globally as of April 18, 2020	108 cases reported as of April 10, 2020[54]	None	Yes[14,54]
Human parainfluenza virus	Very common 50% of children in United States infected by age 1 y	1 case[59]	None	None
Human metapneumovirus	Very common 90%–100% of children infected by ages 5–10 y	20 in cohort study[72] 4 case reports[73–75]	None	None
Respiratory syncytial virus	66.4 million cases globally per year	From 2% to 9.3% of pregnant women with respiratory illness[81,82]	1 neonate with suggested transmission[84]	None
Influenza (including H1N1, H3N2, H5N1, influenza B)	Approximately 1 billion cases globally per year (700 million to 1.4 billion)	Common in unvaccinated pregnant women	4 suspected cases of H1N1[94–97] 1 suspicious case of H5N1[98] Fetal tissues[90–92] Suspected placental infection[93]	Yes[89]

the chorionic villous tree where they enter the fetal circulation.[11,12] Fortunately, not all infectious diseases that occur in women during pregnancy are transmitted to their fetuses—this includes most bacterial infections as well as some viral agents.[11,13] Although no intrauterine transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has yet been reported, there have been adverse outcomes reported in the infants of women with coronavirus disease 2019 (COVID-19), although causality from the infection cannot yet be determined. These include preterm labor and delivery, premature rupture of membranes, intrauterine growth restriction, low birth weight, intrauterine fetal distress, feeding intolerance, asphyxia, pneumonia and respiratory distress, and stillbirth.[14]

The development of the COVID-19 pandemic has resulted in levels of morbidity and mortality throughout the world that have not been seen since the H1N1 influenza pandemic of 1918—it is the deadliest pandemic to have occurred in more than 100 years and its significance as a public health problem continues to increase.[15,16] The causative virus, SARS-CoV-2, is a newly described coronavirus belonging to the family Coronaviridae and genus *Betacoronavirus*, the same genus as 2 previously described coronavirus pathogens of humans that have resulted in previous epidemic disease—SARS-CoV, causing SARS, and Middle East respiratory syndrome coronavirus (MERS-CoV), causing MERS.[17]

SARS-CoV-2 was first identified in December 2019, when it was recognized as the etiologic agent of an outbreak of life-threatening upper and lower respiratory tract infection in Wuhan, Hubei Province, China.[17–19] Since that time the infection has rapidly become a global pandemic, resulting in 152 551 deaths as of April 19, 2020.[15] As is often the case with a newly emergent infection, little is known of the effect of COVID-19 on pregnant women and their infants. There has been global concern for potential intrauterine transmission of SARS-CoV-2 that has resulted in an increasing number of reports of pregnant women with COVID-19 and their neonates.[14,20–28] Although several early-onset neonatal infections have been reported,[29,30] as well as an infant with elevated immunoglobulin (Ig) M antibody to the virus,[31] to date there have been no confirmed cases of intrauterine vertical transmission of SARS-CoV-2. Previous epidemics of related coronavirus diseases—SARS and MERS—resulted in significant maternal and perinatal morbidity and mortality, but although the number of cases of maternal infection was small, there were no confirmed cases of intrauterine maternal-fetal transmission from those 2 pathogens.[17]

"Respiratory viruses" is a colloquial term used to identify viruses that are detected predominantly in patients with respiratory tract infections. Because SARS-CoV-2 and other coronaviruses are RNA viruses whose primary means of transmission is via the respiratory route, we decided to analyze the most pathogenic respiratory RNA viruses that infect humans to evaluate their capabilities of causing disease in pregnant women and, importantly, their potential for intrauterine transmission from an infected woman to the fetus (Table).

SARS AND SARS-CoV

The severe acute respiratory syndrome coronavirus, or SARS-CoV, is an enveloped, positive-sense, single-stranded RNA virus belonging to the family Coronavirdae, genus *Betacoronavirus*. SARS-CoV was the first coronavirus to cause an epidemic. The virus initially emerged as a potentially severe respiratory tract infection during the SARS epidemic of 2002–2003, which began in November 2002 in China's Guangdong Province, where it was initially believed to be an atypical pneumonia or a "flu outbreak." Unfortunately, China failed to report the occurrence of this illness to the World Health Organization until February 2003; by then it had spread within China and to other countries. By July 31, 2003, there were 8422 probable cases, leading to 916 deaths in 29 countries, with most cases occurring in mainland China and Hong Kong. Almost one-

third (30%) of infections occurred in health care workers. By the close of the epidemic the global case fatality rate was 11%.[17,32,33]

Pregnant women who became infected with SARS-CoV were adversely affected. In Hong Kong the clinical outcomes among pregnant women with SARS were worse than among SARS-infected women who were not pregnant.[34] Among a cohort of pregnant women in Hong Kong who developed SARS infection, 4 of the 7 women (57%) who developed SARS during the first trimester sustained spontaneous miscarriages, probably due to the hypoxia that was caused by SARS-related acute respiratory distress. Among a cohort of 5 women who presented after 24 weeks' gestation, 4 had preterm deliveries (80%).[35]

In a case-control study performed to determine the effects of SARS on pregnancy, 10 pregnant and 40 nonpregnant women with SARS were evaluated at the Princess Margaret Hospital in Hong Kong.[32,36] Three deaths occurred among the pregnant women with SARS (maternal mortality rate of 30%), but there were no deaths in the nonpregnant group of SARS-infected women ($P = .006$). Renal failure ($P = .006$) and disseminated intravascular coagulation ($P = .006$) occurred with more frequency in pregnant women with SARS compared with the nonpregnant SARS group. Six pregnant women with SARS (60%) were admitted for intensive care, and 4 (40%) required endotracheal intubation, compared with 12.5% needing intubation ($P = .06$) and 17.5% requiring intensive care ($P = .01$) in the nonpregnant group.

Zhang et al[37] described 5 pregnant women, all primagravidas, from Guangzhou, China, who became infected with SARS at the peak of the epidemic. Of the 5 women, 2 developed infection in the second trimester, and 3 became infected in the third trimester. Two women acquired SARS from the hospital, and the other 3 cases were community acquired. All 5 pregnant women had fever and abnormal chest radiographs; 4 had cough; 4 developed hypoalbuminemia; 3 had elevated alanine aminotransferase levels; 3 had chills or rigor; 2 had decreased lymphocytes; and 2 had decreased platelets. One pregnant woman needed intensive care, but all women recovered and there were no maternal deaths. None of the 5 infants had evidence of SARS.

Yudin et al[38] reported a 33-year-old pregnant woman in Canada with a fever, dry cough, and abnormal chest radiograph demonstrating patchy infiltrates at 31 weeks' gestation. Following a 21-day stay in the hospital, during which she did not require ventilatory support, her convalescent antibody titers were positive for coronavirus infection. She had a normal labor and delivery, and her newborn girl had no evidence of infection.

There were no confirmed cases of intrauterine maternal-fetal transmission of SARS-CoV identified among these and other pregnant women infected with SARS during the 2002–2003 epidemic, although maternal deaths, miscarriages, and preterm deliveries occurred as a result of the infection.[17]

MERS AND MERS-CoV

MERS is caused by a coronavirus—MERS-CoV—belonging to the genus *Betacoronavirus*, similar to SARS-CoV. It is a newly emergent coronavirus that was initially described from Saudi Arabia in September 2012 following its isolation from a man who died months earlier from severe pneumonia and multiple organ failure. Since then there have been more than 2494 confirmed cases of MERS, resulting in upwards of 858 deaths globally.[39] MERS is characterized by sporadic zoonotic transmission events and transmission between infected patients and their close contacts (ie, intrafamilial transmission).[40] Nosocomial outbreaks occurring in health care settings resulting from poor infection control and prevention are widely known to be characteristic of MERS.[39] The clinical presentation of MERS is variable from being asymptomatic to developing severe pneumonia and acute respiratory distress syndrome, septic shock, and multiple organ failure, often resulting in death. Most persons with MERS develop severe acute respiratory illness accompanied by fever, cough, and shortness of breath. Progression to pneumonia is swift with MERS and typically develops within the first week, with at least one-third of patients also presenting with gastrointestinal symptoms. MERS progresses much more rapidly to respiratory failure and has a higher case fatality rate (approximately 34.4%) than does SARS.[39,41] In contrast to infections with SARS-CoV, MERS-CoV produces a generally mild disease in healthy persons but is clinically more severe in patients who are immunocompromised or who have underlying comorbidities.[39]

MERS infections occurring in pregnant women can cause adverse obstetrical outcomes including maternal death, premature delivery, intensive care treatment for newborns, and perinatal death, but similarly to SARS there have been no confirmed cases of transmission of the virus from pregnant woman to fetus.[17] Among 11 pregnant women who became infected with MERS-CoV while pregnant, 10 (91%) developed obstetric complications or had adverse outcomes. These included 6 newborns (55%) needing intensive care, of whom 3 (27%) died, and 2 infants delivered prematurely for severe maternal respiratory failure—no maternal-fetal transmission occurred.[42,43] In another report there were 5 pregnant women among 1308 cases of MERS-CoV infection described by the Saudi Arabia Ministry of Health between November 2012 and February 2016.[44] All 5 women, ranging in age between 27 and 34 years and who had exposure during the second or third trimester, required intensive case and developed poor obstetric outcomes. A total of 2 of the 5 women died, and 2 neonates died, including 1 stillbirth and 1 neonatal death occurring after an emergency cesarean delivery. In Jordan during the 2012 MERS-CoV outbreak in Zarqa, a second-trimester stillbirth (5 months' gestational age) occurred as a result of maternal exposure to MERS-CoV.[45]

SARS-CoV-2 AND COVID-19

Coronavirus disease 2019 (COVID-19) is a novel viral disease caused by a newly identified coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019. SARS-CoV-2 is the seventh coronavirus to cause human infection and is, like SARS-CoV and MERS-CoV, a positive-sense, single-stranded RNA virus and member of the genus *Betacoronavirus*.[15–19] It is also similar to MERS-CoV and SARS-CoV in that it is believed to have zoonotic origins, having a close similarity with bat coronaviruses.[46] As a result of the rapid spread, increasing incidence outside of China, severe and life-threatening features of the infection, and the number of affected countries, the World Health Organization declared the rapid spread of SARS-CoV-2 a pandemic on March 11, 2020.[47]

The clinical features and effects of COVID-19 are currently being studied, and new information is constantly being disclosed. A significant percentage of infected persons are asymptomatic, but this number appears variable and is not exactly known because of issues with surveillance and limitations of testing during the pandemic. Most symptomatic persons develop mild disease resembling an upper respiratory infection, with the most common symptoms being fever, cough, chest tightness, and dyspnea; additional findings can include gastrointestinal symptoms and diarrhea, myalgia, conjunctivitis, sore throat, and neurologic symptoms, including headache, anorexia, lethargy, impaired consciousness, acute cerebrovascular disease, anosmia, and dysgeusia. Severe disease can occur that involves infection of the lower respiratory tract that leads to acute respiratory distress syndrome, respiratory failure, requirement for intensive care and mechanical ventilation, and systemic complications and multiorgan disease, including sepsis, septic shock, and multiorgan dysfunction syndrome.[48,49]

Multiple individual case reports as well as descriptions of cohorts of pregnant women with COVID-19 have been published describing their clinical course, laboratory and radiologic findings, and details of their birthing by cesarean delivery, or, in fewer cases, vaginal delivery.[20–31,50–53] There have now been at least 108 pregnant women with COVID-19 reported, reports that also describe the clinical and laboratory features of most of their newborn infants, including virologic status for SARS-CoV-2.[54] Thus far, there have been no laboratory-confirmed cases of intrauterine transmission of SARS-CoV-2 from an infected pregnant woman to her fetus.[54] There have been a few cases in which early neonatal infection with SARS-CoV-2 has occurred, but because testing of neonates was delayed from 30 hours to 2 days following delivery it cannot be definitively established that they developed COVID-19 prior to delivery, and their infection may have occurred in the interval between delivery and testing.[29,53] In a single case laboratory, testing of a newborn performed at 2 hours following delivery from a mother with COVID-19 revealed that the infant had developed IgM- and IgG-specific antibodies to SARS-CoV-2 together with elevated cytokines, but multiple nasopharyngeal swabs from the infant were negative for the virus.[31] A variety of specimens have also been tested using reverse transcriptase–polymerase chain reaction (RT-PCR) for the presence of SARS-CoV-2 following delivery of women with COVID-19—these include placenta, umbilical cord blood, amniotic fluid, maternal blood, vaginal secretions, and breast milk—and all have been negative for the virus.

Although no intrauterine transmission of the virus has yet been reported, there have been adverse outcomes occurring in the infants of women with COVID-19. These include preterm labor and delivery, premature rupture of membranes, intrauterine growth restriction, low birth weight, intrauterine fetal distress, feeding intolerance, asphyxia, pneumonia, and respiratory distress. However, because of multiple factors, including comorbid conditions existing in the mother and fetus, small sample size, and the lack of fetal and placental infection, it is difficult at this time to ascribe one or more of these outcomes directly to COVID-19 with any certainty. There has been 1 case of an adverse fetal outcome that is ascribable to maternal SARS-CoV-2 infection—a stillborn infant whose mother developed severe complications of COVID-19, including pneumonia requiring mechanical ventilation, extracorporeal membrane oxygenation, and multiorgan dysfunction syndrome.[21] In that case, although there was a fetal death, the infant was reported as being negative for infection. There have been no reports of adverse effects of COVID-19 in pregnant women during the first trimester, and it currently remains unknown whether this infection will be associated with miscarriages and early pregnancy losses, as are SARS and MERS.[17]

Maternal complications from COVID-19 infection have been reported that are similar to those occurring in nonpregnant adults. For those pregnant women who developed respiratory disease it has been typically non–life-threatening, including pneumonia accompanied by radiologic findings of patchy pulmonary infiltrates, ground-glass opacities, and consolidation.[55] However, in a few cases there have been pregnant women with COVID-19 who have developed severe pneumonia and life-threatening disease. In a report from New York City the infection status of 2 pregnant women was unknown until after delivery, when they developed medical complications, were admitted for intensive care, and were found to have COVID-19—their infants were negative for the virus.[56]

PARAINFLUENZA VIRUS

Human parainfluenza viruses are enveloped, single-stranded RNA viruses belonging to the family Paramyxoviridae. There are 4 types of HPIVs (types 1 through 4) and 2 subtypes (4a and 4b). Parainfluenza viruses can cause a wide spectrum of respiratory tract illnesses, including conjunctivitis, otitis media, pharyngitis, croup, tracheobronchitis, and pneumonia. Among children younger than 5 years, HPIVs are the second most frequent cause of acute respiratory illness leading to hospitalization—they are ahead of influenza viruses and exceeded only by RSV.[57] Epidemics of HPIVs can occur seasonally, where they account for up to 40% of pediatric hospitalizations for lower respiratory tract infections and 75% of croup cases.[58] Human parainfluenza viruses can also produce infections in adults, especially the elderly and those who are immunocompromised.

Although there is scant information available on the effects of HPIV infection occurring during pregnancy, there has never been a confirmed report of intrauterine transmission of the virus to a fetus. In one case report from 1996, a multigravida with a previous history of 3 missed abortions had an elective termination of pregnancy at 22 weeks' gestation for fetal ventriculomegaly and hydrocephalus.[59] She had developed increasing antibody titers to HPIV type 3, but no respiratory symptoms were mentioned. Following the termination procedure pathologic examination of the placenta showed no abnormalities, but the autopsy revealed lungs with multiple areas of pneumonia, necrosis, and an inflammatory reaction consisting primarily of mononuclear cells but also neutrophils and giant cells. In retrospect, it is difficult to ascribe any of the findings in this fetus to HPIV infection with any degree of confidence.

Young infants have serum IgG antibodies against HPIVs that are derived from the pregnant woman during gestation. These antibodies are transferred across the placenta during the last trimester of pregnancy and can provide some protection during the first months of extrauterine life.[57,60]

METAPNEUMOVIRUS

Human metapneumovirus is an enveloped, nonsegmented, negative-sense, single-stranded RNA virus that is

a member of the new virus family Pneumoviridae, created in 2016 as a member of the order Mononegavirales.[61] There are currently 5 species in this family that are divided into 2 genera—*Metapneumovirus* and *Orthopneumovirus*.[62] In addition to the hMPV the family Pneumoviridae includes another important respiratory pathogen of humans, RSV, also termed the human orthopneumovirus. There are 2 main genotypes (A and B), as well as at least 4 genetic subtypes (A1, A2, B1, and B2) of hMPV.[63]

Following its discovery in 2001 from stored nasopharyngeal specimens taken from children with respiratory disease,[64] hMPV has been recognized to be a common cause of upper and lower respiratory infections, especially in children, as well as among immunocompromised persons and the elderly.[63,65–67] Human metapneumovirus causes approximately 5% to 25% of all respiratory infections in infants and children, and is responsible for between 5% and 15% of childhood hospitalizations for lower respiratory tract disease.[68–70] The infection is so prevalent that virtually all children will have been infected with hMPV by the time they reach 5 years of age.[71]

There are few data available on hMPV during pregnancy. Among nonasthmatic pregnant women with upper respiratory tract infections, 17.2% were positive by PCR for hMPV.[72] The median duration of maternal symptoms in a study from Nepal was 5 days, and almost one-half (43.6%) of pregnant women with hMPV also had a viral coinfection, most frequently due to rhinovirus and followed by coronavirus and parainfluenza.[69] Birth outcomes in the Nepal study revealed no differences in birth weight or frequency of premature delivery between infants from pregnant mothers with and without hMPV infection. However, women having hMPV infection during pregnancy were 1.7 times ($P = .03$) more likely to have a small-for-gestational age newborn compared with uninfected women. No mothers developed severe pulmonary disease, and there were no cases of newborns reported with respiratory infection.

There have been 4 case reports of hMPV infection occurring in pregnant women, none of whom transmitted hMPV to their fetus.[73–75] Emont et al[73] reported 2 pregnant women with confirmed hMPV infection. In the first case a 40-year-old pregnant woman with a respiratory panel positive only for hMPV infection received intensive care for respiratory decompensation—she had an uncomplicated vaginal delivery of a 3600-g female infant with no signs of infection. In the second case a 36-year-old gravida 4, para 2 woman at 31 weeks' gestation developed respiratory symptoms, a respiratory pathogen panel was positive only for hMPV infection, and she later delivered a healthy, 3230-g baby girl at 39 weeks' gestation with no respiratory infection. Haas et al[74] described a 24-year-old pregnant woman at 30 weeks' gestation with fever and urinary tract infection that progressed to respiratory insufficiency; she delivered a baby girl 6 weeks later with no evidence of infection. Fuchs et al[75] described an 18-year-old pregnant woman at 36 weeks 2 days' gestation with multiple comorbid conditions and severe respiratory disease requiring intensive care. Following a cesarean delivery, her respiratory viral panel was found to be positive for hMPV. The neonate required face mask ventilation during the initial few minutes of life, but she quickly stabilized and had no evidence of hMPV infection.

RESPIRATORY SYNCYTIAL VIRUS

Human RSV, also known as human orthopneumovirus, is an enveloped, nonsegmented negative-sense RNA virus of the *Pneumovirus* genus, Pneumovirinae subfamily, and Paramyxoviridae family.[76] Respiratory syncytial virus shares the Paramyxoviridae family with such prevalent pathogens as parainfluenza, measles, and mumps viruses. Respiratory syncytial virus is divided into 2 groups, termed A and B, that are based upon variability in the antigen reactions against viral fusion (F) and attachment (G) glycoproteins.[77]

This virus was first described in 1901 as "acute catarrhal bronchitis."[78] Respiratory syncytial virus is the most common respiratory pathogen in infants and young children, with an incidence of 33.1 million acute lower respiratory tract infections, 3.2 million hospital admissions, and 59 600 in-hospital deaths in children younger than 5 years. Infants younger than 6 months account for 45% of RSV-related hospitalizations and deaths.[79] Respiratory syncytial virus has been experimentally demonstrated to cross the rodent placenta from the respiratory tract of an infected dam to infect the lungs of the fetal rats.[80]

Maternal RSV infections are generally uncommon and constitute from 2% to 9.3% of women with symptomatic respiratory illnesses.[81,82] One study found that pregnant women testing positive for RSV had symptoms averaging 3 days with presentation of fever, cough, and/or rhinorrhea. Respiratory syncytial virus subtype A made up most of these cases and showed coinfection with viruses such as coronavirus, rhinovirus, parainfluenza 2, hMPV, and bocavirus.[81] There were no maternal deaths; all 7 infants were liveborn and with some complications occurring, including low birth weight (1 case) and preterm delivery (2 cases), that were close to an expected rate in noninfected patients.

Although RSV annually infects tens of millions of persons, there have just been 2 reports suggestive of intrauterine transmission of the virus—one based on cord blood analysis by PCR and the other a symptomatic neonate. A retrospective study has shown low levels of PCR-detectable RSV nucleic acid in 57.7% of umbilical cord blood samples of infants from RSV-positive mothers; however, there was no overt disease noted in the infants.[83] One case of suspected intrauterine RSV infection has been reported in which a preterm infant (35 weeks) was delivered via cesarean delivery for reduced fetal movement; following delivery he had symptoms and imaging studies suggestive of respiratory distress syndrome. The neonate required ventilatory support and was found to be positive for anti-RSV IgM, IgA, and IgG titers. An RSV PCR was positive, whereas 40 other viral and bacterial respiratory pathogens were negative. Maternal RSV was also positive for anti-RSV IgM, IgA, and IgG, which was consistent with maternal complaints of cough during the second trimester of pregnancy. Breast feeding was withheld, the infant improved at 17 days of life, and then tested negative for RSV.[84]

INFLUENZA

Influenza viruses A and B are enveloped, single-stranded RNA viruses belonging the family Orthomyxoviridae. Influenza type A, responsible for most seasonal cases and pandemics, is able to undergo periodic antigenic shifts of glycoproteins, haemagglutinin (H), and neuraminidase (N), leading to several subtypes.[85] Influenza-like illnesses have been reported since 412 BC, with large-scale pandemics including the 1918 "Spanish flu," 1958 "Asian flu," 1968

"Hong Kong flu," and the 2009 "Swine flu" pandemic. Influenza is a highly contagious respiratory virus which infects up to approximately 10% (1 billion) of the global population each year. In the United States it is the seventh leading cause of death and is estimated to have caused between 9 million and 45 million illnesses, 140 000 to 810 000 hospitalizations, and 12 000 to 61 000 deaths annually since 2010.[86] Annual influenza vaccination guidelines have led to the significant decrease in morbidity and mortality for both mothers and infants up to 6 months of life.[87]

Pregnant and recently postpartum women are more likely to develop severe complications from influenza than are nonpregnant adults, including progression to pneumonia, need for hospitalization, intensive care admission, maternal death, and adverse perinatal and neonatal outcomes.[88] Pregnant women with influenza are 4 to 18-times more likely to require hospitalization than are nonpregnant infected women.[89] For the fetus, maternal influenza infection causes increased risk of pregnancy loss, stillbirth, preterm birth, neonatal intensive care unit admission, growth restriction, and neonatal death.

Extensive surveillance, case reporting, and research have demonstrated that influenza virus does cross the placenta, but considering the tremendous prevalence of the infection, intrauterine fetal infection is at most infrequent and, more probably, rare. Evidence for intrauterine influenza transmission of influenza exists from antigen and antibody testing in the infant brain, amniotic fluid, fetal heart, and cord blood,[90–92] and another report found 3 of 186 placentas had positive viral antigen testing and notable pathologic changes to the placenta.[93]

During the 2009 H1N1 (swine flu) pandemic an estimated 11% to 21% (700 million to 1.4 billion people) of the world population became infected, and there were 4 case reports of suspected H1N1 vertical transmission in newborns of infected mothers.[94–97] All 4 infants were delivered by cesarean delivery, had severely ill mothers positive for H1N1, and were tested immediately after birth, prior to contact with the mother. An infant born at 36 weeks tested positive for H1N1 after his mother had respiratory failure and required assisted ventilation.[94] A preterm newborn was born at 31 weeks with postnatal findings of respiratory distress and tested positive for H1N1; her mother had cardiopulmonary failure and died on day 7.[95] In the third report, a full-term newborn had a throat swab positive by RT-PCR for H1N1 after developing respiratory distress requiring ventilatory support on day 1; her mother had respiratory distress and required ventilatory support for 14 days.[96] A fourth case involved a newborn born at 32 weeks who tested positive for H1N1 and also required intubation for respiratory distress.[97]

In 2012 a pregnant woman in the Sóc Trăng Province of Vietnam died from complications of influenza H5N1 at 36 weeks' gestation.[98] Her newborn was delivered by cesarean delivery and developed early-onset neonatal pneumonia; throat swabs and paired serum samples from the infant were negative for the virus.

In addition to these reports from humans, experimental animal studies have also suggested the potential for transplacental transmission of H3N2, H5N1, and influenza B.[99]

DISCUSSION

Even before the emergence of SARS-CoV-2 as a cause of COVID-19 and pandemic pneumonia, respiratory infections caused by RNA viruses were some of the most prevalent infectious diseases and posed significant public health problems for many decades. Although influenza causes close to 1 billion annual infections worldwide, noninfluenza RNA virus infections have also been important contributing sources of morbidity and mortality.[100] It is fortunate that among pregnant women having viral infections, most viruses do not cross the placental barrier, but when they do, they can cause devastating fetal illness, including birth defects, miscarriage, abnormalities of growth and development, neurologic injuries, fetal death, preterm delivery, and neonatal complications. In past epidemics of viral disease, pregnant women and their infants have frequently had the poorest outcomes of any group, especially in those situations where specific antiviral medications and effective vaccines were nonexistent or unavailable.

As SARS-CoV-2 rapidly spread from Wuhan, China, creating the COVID-19 pandemic, there has understandably been a high degree of concern and anxiety about its effects on pregnant women, fetuses, and neonates. Fortunately, as increasing data have become available on the effects of SARS-CoV-2 during pregnancy it is becoming more evident that most pregnant women with COVID-19 will not develop severe or life-threatening illness. However, a small minority of pregnant women are having, and will continue to develop, severe disease both during and following pregnancy,[101,102] similar to the severe and life-threatening illness from COVID-19 occurring in some infected nonpregnant women in the reproductive age group. At this time, it is too early to know if pregnant women have a differing susceptibility to developing symptomatic infection or clinical disease spectrum compared with those infected women who are not pregnant.

No cases of confirmed intrauterine transmission of SARS-CoV-2 have yet to be reported from pregnant women with COVID-19.[14,54] This is not unexpected; during previous epidemics of infections caused by 2 related coronaviruses—SARS-CoV and MERS-CoV—there were also no cases of intrauterine viral transmission to the fetus.[17] Although the numbers of infected pregnant women were small, both SARS and MERS did result in both maternal as well as perinatal morbidity and mortality.[17] Similarly to coronaviruses, other respiratory RNA viruses are not easily transmitted from infected mothers to their fetus. Metapneumovirus and parainfluenza virus are widely prevalent pathogenic RNA respiratory viruses that have never been documented to demonstrate maternal-fetal transmission. Respiratory syncytial virus, a seasonally prevalent respiratory RNA virus that infects both children and adults, has been associated with just 2 episodes of potential intrauterine transmission. Influenza viruses, the prototypical respiratory RNA viruses producing epidemics and pandemics, have been described to infect the placenta and the fetus in several reports. Placed in context, however, influenza causes almost 1 billion infections per year, and when compared with the few reports of intrauterine infection that have been described, transplacental passage of this virus is probably an exceedingly rare event.

The factors inherent in this observed inhibition of respiratory RNA viruses to undergo intrauterine vertical transmission reside in both the virus as well as the host, and a detailed analysis is beyond the scope of this communication to discuss. At the host level, the maternal-fetal interface, composed of cells of both maternal and fetal origin, is one of the most significant factors in determining

the propensity of infectious agents to undergo maternal-fetal transmission. The placenta is a key component of this maternal-fetal interface, acting as a barrier between the maternal and fetal compartments. In addition to its functions in producing hormones that support the pregnancy and in organizing placental transport functions, the syncytiotrophoblast immunologically defends the fetus from a variety of infectious agents. Its location at the surface of the chorionic villi, in direct contact with the mother's blood circulating in the intervillous space, is optimal for interacting with both maternal and fetal microenvironments in order to physically and immunologically form a barrier to infection. Experimental studies have demonstrated that not only are primary human trophoblasts resistant to infection by a variety of viruses,[103] but they also can transfer resistance in cell culture to both RNA and DNA viruses of perinatal significance.[104] This viral resistance is at least partially mediated by microRNAs (miRNAs, small noncoding RNAs approximately 22 nucleotides in length) from the chromosome 19 miRNA cluster (C19MC). This is the largest miRNA cluster occurring in humans and is almost exclusively expressed in the placenta.[105] C19MC miRNAs are highly expressed in exosomes released from primary human trophoblast cells and are present in the plasma of pregnant women.[106] In addition, there is experimental evidence that primary human trophoblasts release type III interferon IFNλ1, a signaling protein that functions in both an autocrine and a paracrine manner to protect trophoblast and nontrophoblast cells from infections with specific viruses.[107]

Following access to the gravid uterus through the maternal bloodstream, passage of a virus is not only dependent on the avoidance of such protective factors as the innate immune system and the placental syncytiotrophoblast barrier, but also on its tropism for cells at the maternal-fetal interface. For SARS-CoV-2, the spike (S) protein of the virus has been demonstrated to facilitate its entry into host cells. This process is dependent on binding of the surface unit, S1, of the S protein to a cellular receptor, which facilitates viral attachment to the surface of target cells.[108] It is currently believed that the cell receptor for SARS-CoV-2 is angiotensin-converting enzyme 2, termed ACE-2.[46] ACE-2 is a type I transmembrane metallocarboxypeptidase that is expressed in cells of the lung, kidney, and gastrointestinal tract, these tissues being targets of SARS-CoV-2.[109] Viral entry into a host cell requires the priming of the S protein by cellular proteases, in which the S protein is cleaved at the S1/S2 and the S2′ site. The serine protease TMPRSS2 is necessary for S protein priming.[110] This process permits the fusion of viral and cellular membranes, a process driven by the S2 subunit. One of the factors that will regulate transmissibility of SARS-CoV-2 from the mother to her fetus will likely be the availability of cells at the maternal-fetal interface bearing the ACE-2 receptor and having the necessary associated enzymes such as TMPRSS2S to facilitate viral binding.[108]

Placental pathology has proven to be a useful technique for understanding the nature of and potential risk factors for maternal-fetal infection. Some TORCH infections, which have an association with increased likelihood of fetal transmission in early gestation, have been associated with such inflammatory placental abnormalities as villitis, chronic histiocytic intervillositis, and Hofbauer cell hyperplasia. These pathology abnormalities are not typically present in the placentas of women with respiratory RNA infections. If and when intrauterine transmission of SARS-CoV-2 occurs, examination of the placenta will be of critical importance in localization of the virus and characterization of the spectrum of microscopic abnormalities that result from placental infection, as has previously been performed with TORCH infections, and Zika and Ebola virus diseases.

Although research is in progress to better understand the effects of COVID-19 on pregnant women and the fetus, it appears that if intrauterine transmission of SARS-CoV-2 does eventually occur, it will likely be a rare event and that most fetuses will be uninfected at the time of their birth.

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