Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

An update on COVID-19 and pregnancy

Denise J. Jamieson, MD, MPH; Sonja A. Rasmussen, MD, MS

Physiological, mechanical, and immunologic alterations in pregnancy could potentially affect the susceptibility to and the severity of COVID-19 during pregnancy. Owing to the lack of comparable incidence data and the challenges with disentangling differences in the susceptibility from different exposure risks, the data are insufficient to determine whether pregnancy increases the susceptibility to SARS-CoV-2 infection. The data support pregnancy as a risk factor for severe disease associated with COVID-19; some of the best evidence comes from the United States Centers for Disease Control and Prevention COVID-19 surveillance system, which reported that pregnant persons were more likely to be admitted to an intensive care unit, require invasive ventilation, require extracorporeal membrane oxygenation, and die than nonpregnant women of reproductive age. Although the intrauterine transmission of SARS-CoV-2 has been documented, it appears to be rare. It is possibly related to low levels of SARS-CoV-2 viremia and the decreased coexpression of angiotensin-converting enzyme 2 and transmembrane serine protease 2 needed for SARS-CoV-2 entry into cells in the placenta. Evidence is accumulating that SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes including preeclampsia, preterm birth, and stillbirth, especially among pregnant persons with severe COVID-19 disease. In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on healthcare systems have had adverse effects such as increased stillbirths and maternal deaths on the pregnancy outcomes. These trends may represent widening disparities and an alarming reversal of recent improvements in maternal and infant health. All the 3 COVID-19 vaccines currently available in the United States can be administered to pregnant or lactating persons, with no preference for the vaccine type. Although the safety data in pregnancy are rapidly accumulating and no safety signals in pregnancy have been detected, additional information about the birth outcomes, particularly among persons vaccinated earlier in pregnancy, are needed.

Key words: COVID-19, fetal death, fetus, maternal death, newborn, perinatal infection, pneumonia, pregnancy, preterm birth, SARS-CoV-2, vertical transmission

Introduction

Since the identification of the first cases of COVID-19 caused by infection with SARS-CoV-2 in Wuhan, China in December 2019, the virus has spread rapidly throughout the world. Worldwide, over 207 million persons have been infected with more than 4 million deaths. In the United States alone, over 620,000 persons have died of COVID-19 as of August 15, 2021.[1] In addition to the devastating degree of morbidity and mortality caused by SARS-CoV-2, the virus and the efforts to mitigate its transmission have caused unprecedented economic and social disruption. Early on, many questions arose regarding the effects of COVID-19 on pregnant persons, including whether pregnancy increased susceptibility to SARS-CoV-2 infection, whether pregnant persons were more likely to have severe disease, and whether SARS-CoV-2 infection increased the risk of adverse pregnancy and neonatal outcomes. Here, we review the latest information on SARS-CoV-2 infection during pregnancy, including what is known about the use of COVID-19 vaccines during pregnancy and lactation.

From the Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA (Dr Jamieson); Departments of Pediatrics (Dr Rasmussen) and Obstetrics and Gynecology (Dr Rasmussen), University of Florida College of Medicine, Gainesville, FL; and Department of Epidemiology, University of Florida College of Public Health and Health Professions and College of Medicine, Gainesville, FL (Dr Rasmussen).

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Corresponding author: Denise J. Jamieson, MD, MPH. djamieson@emory.edu

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Susceptibility, severity and clinical course

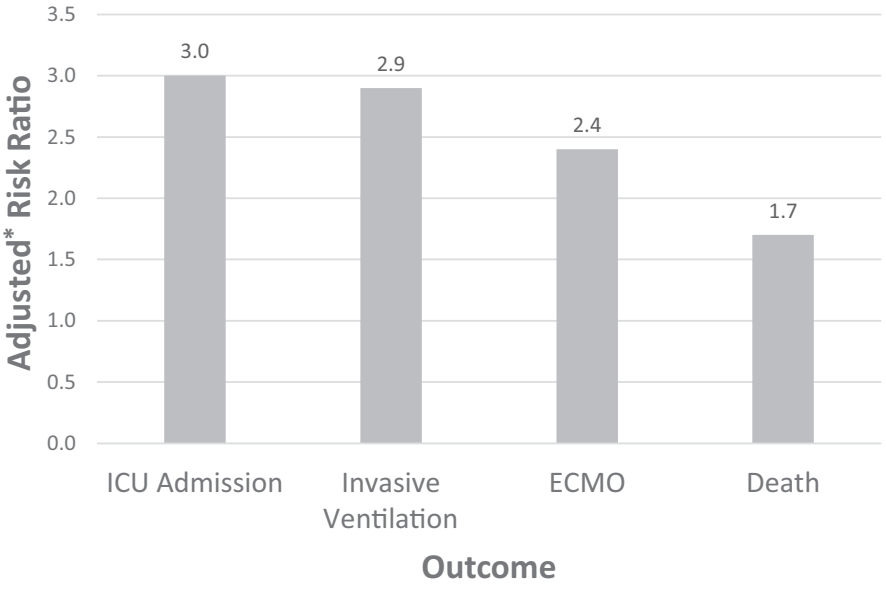
Although physiological, mechanical, and immunologic alterations in pregnancy could potentially affect susceptibility to COVID-19 during pregnancy, limited data are available to address this issue. Many studies have reported the prevalence of SARS-CoV-2 infection among pregnant persons presenting to labor and delivery, with estimates ranging from 3−20%.[2,3] However, it is difficult to compare these rates to other populations, because universal screening is not commonly conducted. One study compared universal preprocedural testing among asymptomatic surgical patients to obstetrical patients presenting in labor. The asymptomatic infection rate was 15-fold higher in obstetrical patients than that in surgical patients even after adjustment for age, race, and sex.[4] In a report from the US Centers for Disease Control and Prevention (CDC), the number of cases of laboratory-confirmed SARS-CoV-2 infection was higher than expected among pregnant persons; among women of reproductive age infected with SARS-CoV-2, 9% were pregnant compared with an estimated 5% of women aged 15 to 44 years who are pregnant at any point in time. However, there were large amounts of missing data, and the investigators were unable to adjust for potentially different testing and ascertainment rates, given more widespread screening of asymptomatic pregnant persons.[5] Similarly, a

study from Washington state reported higher infection rates among pregnant patients (13.9 per 1000 deliveries) than nonpregnant adults aged 20 to 39 years (7.3 per 1000 persons); this study was also unable to account for the differential testing rates in pregnant compared with nonpregnant persons.[6] Even with better incidence data, disentangling the differences in susceptibility from different exposure risks is challenging. To address susceptibility, the incident rates of infection among pregnant and nonpregnant women of the same age with similar exposures to SARS-CoV-2 would ideally be compared. In summary, the data are insufficient to conclude whether or not pregnancy increases susceptibility to SARS-CoV-2.

Similar to what is observed in nonpregnant persons, SARS-CoV-2 infection is more frequent among the persons who live in socially and economically disadvantaged settings. In a report from New York City, the likelihood of SARS-CoV-2 infection was higher in pregnant persons who lived in buildings with lower mean assessed values and more residential units. It was also higher in the neighborhoods with lower median household incomes, higher unemployment rates, large household sizes, and greater household crowding.[7] In a report from Atlanta, higher rates of SARS-CoV-2 infection among pregnant persons were associated with Hispanic ethnicity, lack of health insurance, high neighborhood density, and paradoxically, smaller household size.[8]

Several studies support that COVID-19 causes more severe disease during pregnancy. Although many early reports lacked appropriate comparison groups, later studies have compared pregnant with nonpregnant women, adjusted by age and comorbidities. Some of the best data come from the CDC's COVID-19 surveillance system, which included over 400,000 persons of reproductive age with symptomatic COVID-19 and adjusted for age, race and ethnicity, and underlying medical conditions. Compared with nonpregnant women, pregnant persons were 3 times more likely to be admitted to an intensive care unit (ICU) (10.5 vs 3.9 per 1000), 2.9 times more likely to require invasive ventilation (2.9 vs 1.1 per 1000 cases), 2.4 times more likely to require extracorporeal membrane oxygenation (0.7 vs 0.3 per 1000 cases), and 1.7 times more likely to die (1.5 vs 1.2 per 1000 cases)[9] (Figure). Additional studies from the United States and Europe report similar results. For example, a study from 4 European hospitals compared pregnant and nonpregnant women matched by the propensity score for age, body mass index, and comorbidities and found an increased risk of severe disease during pregnancy, including an increased risk of ICU admission (primary outcome). The study also found increased risks of hospital admission, need for oxygen therapy, and need for endotracheal intubation (secondary outcomes) in infected pregnant women.[10] A study from Washington state found an increased risk of hospitalization and an elevated case-fatality rate among pregnant persons compared with nonpregnant persons of similar age.[11] The increased risk for disease severity in pregnancy may be owing to mechanical changes such as decreased lung volume as the fetus grows, immunologic changes, and an increased risk for thromboembolic disease.[9]

FIGURE
Risk of severe COVID-19 among pregnant persons compared with nonpregnant women[9]



ECMO, extracorporeal membrane oxygenation; *ICU*, intensive care unit. *Adjusted by age, race and ethnicity, and underlying medical conditions.

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The risk factors for severe disease have been shown to be similar among pregnant and nonpregnant persons. Data from the United Kingdom's Obstetric Surveillance System found that black race, older age (≥35 years), and being overweight or obese were the risk factors for hospitalization among pregnant persons.[12] Similarly, the data from the Surveillance for Emergency Threats to Mothers and Babies Network in the United States found that older age and underlying medical conditions such as obesity, chronic lung disease, chronic hypertension, and pregestational diabetes mellitus were associated with more severe COVID-19 in pregnancy.[13] A report from the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network found that older maternal age, higher body mass index, and preexisting comorbidities defined as asthma, chronic obstructive pulmonary disease,

chronic hypertension, or pregestational diabetes mellitus were associated with more severe COVID-19 disease during pregnancy.[14] Similar to nonpregnant persons, certain chronic medical conditions may lead to increased COVID-19 disease severity in a variety of ways such as weakening the immune system, increasing inflammation, or reducing the ability to withstand infection. Regarding the clinical course, a prospective registry of pregnant patients with symptomatic COVID-19 found that 25% of pregnant patients reported persistent symptoms 8 or more weeks from symptom onset.[15] Whether pregnancy confers an increased risk for a prolonged course of disease requires additional study.

Transmission of SARS-CoV-2 to the fetus and neonate

When a new virus emerges, a critical question that arises is whether the virus can cross the placenta and cause direct adverse effects on the fetus as has been seen with several other pathogens (eg, Zika, cytomegalovirus, rubella). The transmission of pathogens can occur during pregnancy and before the onset of labor (intrauterine); during labor and delivery (intrapartum); or following birth, either through breastfeeding or through contact with the mother or others (postpartum). Several systems have been developed to categorize perinatal SARS-CoV-2 transmission, and they share some common features, including requiring the evidence of maternal infection, fetal exposure, and persistence of infection in the fetus or neonate.[16–18] Although a few cases of intrauterine SARS-CoV-2 transmission have been carefully documented,[19] transmission appears to be rare.[18] Several factors may help explain why transmission appears to be rare. For the intrauterine transmission of a viral pathogen to occur, the pathogen needs to reach and cross the placenta,[20] and SARS-CoV-2 infection is not associated with high levels of viremia.[21] In addition, the placenta may not coexpress high levels of the primary factors that facilitate SARS-CoV-2 entry into cells, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2)[21–23], although the data regarding the expression of these factors are not entirely consistent.[24,25]

Most SARS-CoV-2 infections identified among infants after birth are owing to exposure to infected caregivers. However, the data on the safety of a SARS-CoV-2-infected mother breastfeeding are reassuring. Replication-competent SARS-CoV-2 has not been detected in breastmilk,[26] although breastmilk samples are occasionally polymerase chain reaction–positive.[27] An observational cohort of 116 SARS-CoV-2-infected mothers who reported consistent use of surgical masks, hand hygiene, and breast cleansing, all safely breastfed without SARS-CoV-2 transmission.[28] In addition, a systematic review found no increase in late postnatal transmission (defined as occurring after 72 hours of life) associated with breastfeeding. However, an increased risk of late postnatal transmission was observed when the infants were not separated from their infected mothers after birth.[29] This possible increased risk must be weighed against the known benefits of mother-infant bonding and the minimal risk of severe infant illness. Most guidelines support the rooming in of the newborn with an infected mother, particularly when the mother is afebrile and asymptomatic.[30,31]

Pregnancy outcomes

Although it appears that SARS-CoV-2 is rarely transmitted transplacentally to the fetus, evidence that SARS-CoV-2 infection during pregnancy is associated with a number of adverse pregnancy outcomes is accumulating. A systematic review and meta-analysis of relatively high-quality studies with appropriate comparison groups found an increased risk of preeclampsia, preterm birth, and stillbirth among pregnant persons with SARS-CoV-2 infection than in those without SARS-CoV-2 infection.[32] Among pregnant persons with COVID-19, severe disease was associated with preeclampsia, preterm birth, gestational diabetes, and low birthweight compared with those with mild disease.[32] Two studies published after the meta-analysis found similar findings. A multinational cohort study found that pregnant persons with COVID-19 were at increased risk for preeclampsia/eclampsia and preterm birth than pregnancies without COVID-19.[33] In an observational study of 1219 pregnant patients testing positive for SARS-CoV-2, those with severe disease were at an increased of cesarean delivery, hypertensive disorders of pregnancy, and preterm birth compared with asymptomatic patients.[14]

In addition to the direct impact of COVID-19 on pregnancy outcomes, there is evidence that the pandemic and its effects on healthcare systems have had adverse effects on pregnancy outcomes even among those not infected with SARS-CoV-2. In a global systematic review, increases in the stillbirths and maternal deaths, declines in maternal mental health (as measured by the mean Edinburgh Postnatal Depression Scale scores), and an increased rate of ruptured ectopic pregnancies representing a delay in appropriate care were observed during the pandemic than before the pandemic.[34] This deterioration in several maternal health measures, which was more pronounced in low-resource settings than in high-resource settings, may represent widening disparities and an alarming reversal of recent improvements in maternal and infant health.[35] Paradoxically, an overall decline in the preterm birth rates was seen during the pandemic lockdown periods in some[36–40] but not all[41,42] high-resource settings, largely owing to reductions in extreme prematurity. Although these trends could represent a shift in deliveries from liveborn premature infants to stillborn infants, these may alternatively represent true improvements in the birth outcomes in some settings. Because our efforts over many decades to prevent preterm birth have been largely unsuccessful, these findings are intriguing and could potentially hold the clues to address the long-standing challenges in preventing preterm births.

Management of COVID-19 infection in pregnancy

In general, the clinical management of pregnant persons with COVID-19 is

similar to that of nonpregnant persons, and effective treatments should not be withheld based on the pregnancy status.[43] For example, antiviral therapy with remdesivir should not be withheld if otherwise indicated even with limited albeit reassuring safety data.[44] Several types of monoclonal antibodies have been authorized for the treatment of symptomatic COVID-19 patients who are at a high risk of progressing to severe COVID-19 and/or hospitalization. Because pregnancy is included as a risk for clinical progression, pregnant patients are eligible to receive outpatient monoclonal antibodies under Emergency Use Authorization. Dexamethasone is recommended for patients with COVID-19 who are mechanically ventilated or require supplemental oxygen; this includes pregnant women. Prophylactic anticoagulation is recommended for hospitalized patients with COVID, and this includes pregnant patients. Although other therapeutic options for COVID-19 are being evaluated, many clinical trials for novel therapeutic agents exclude pregnant persons.[44,45]

Although the clinical algorithms for treating COVID are similar in pregnant and nonpregnant persons, there are some important differences. The oxygen saturation in pregnancy should be maintained at 95% or greater on room air, so that the threshold for admitting pregnant patients may be lower than that for nonpregnant patients. In addition, the scoring systems to assess clinical deterioration and the need for admission to an ICU have not been well-validated in pregnant persons. Therefore, the algorithms specifically tailored for pregnancy may be helpful. Prone positioning has been shown to be of benefit for some COVID patients, such as those who are mechanically ventilated; the prone position is safe in pregnancy and can be safely achieved with some possible modifications such as positioning in the left lateral decubitus position.[45]

In general, COVID is not an indication for delivery and should neither alter the timing nor the mode of delivery. However, in some cases where the delivery is not medically indicated, it may be delayed until the mother tests negative for COVID to decrease the likelihood of transmission to the neonate.[43]

The clinical guidelines for the management of pregnant patients with COVID have been developed by the National Institutes of Health and the Society for Maternal and Fetal Medicine (SMFM). They are regularly updated and provide an excellent source for up-to-date information.[44,45]

COVID-19 vaccination in pregnant and lactating persons

The following 3 COVID-19 vaccines are currently available: 2 mRNA vaccines (from Pfizer-BioNTech, New York, NY and Germany Moderna, Cambridge, MA) and one adenoviral vector vaccine (Johnson & Johnson—Janssen, Belgium) (Table). The CDC specifies that any of the currently authorized vaccines can be administered to pregnant or lactating persons, with no preference for the vaccine type.[54] The American College of Obstetricians and Gynecologists (ACOG), the SMFM, and the CDC strongly recommend that pregnant and lactating persons be vaccinated. The ACOG further specifies that pregnant persons should be encouraged to talk to their obstetrical healthcare provider about their vaccination plan and discuss any questions they have. However, this should not be a requirement for vaccination, because it could serve as a barrier. Pregnant patients who decline vaccination should be reoffered the vaccine and should be reminded about the importance of continuing other prevention measures such as wearing a mask and physical distancing.[43] ACOG guidance also does not state a preference for the vaccine type or for the timing of vaccination during pregnancy.[43] In the United Kingdom, the Royal College of Obstetricians & Gynaecologists recommends an mRNA vaccine for pregnant persons, because there are more safety data available for the mRNA vaccines than for the adenoviral vaccine.[55] This may have implications for the countries where only adenoviral vaccines are available. The CDC recently reported that among nearly 136,000 pregnant persons who had not completed COVID-19 vaccination before pregnancy, only 16% received ≥1 dosage of the vaccine, and 11% had completed vaccination during pregnancy. COVID-19 vaccination during pregnancy was the lowest among persons of Black and Hispanic race and among younger women (aged 18—24 years). Pregnant persons were less likely to be vaccinated than nonpregnant women of reproductive age.[56]

Although the safety data in pregnancy were limited when these vaccines were first available in the United States, they are rapidly accumulating. Nearly 150,000 pregnant persons have signed up for V-safe, the CDC's smartphone-based tool that uses text messaging and web-based surveys to collect information from those who have received a COVID-19 vaccine; more than 5000 pregnant persons have enrolled in the V-safe pregnancy registry, which follows pregnant persons and their infants until 3 months after pregnancy completion.[57] In a preliminary analysis of pregnant persons who received an mRNA vaccine, no concerning safety signals were seen. The analysis included 35,691 pregnant persons who registered for V-safe and 3,958 pregnant persons who enrolled in the registry (including 827 with a completed pregnancy). Although there were a few small differences, pregnant persons and nonpregnant women had similar reactogenicity profiles. Pregnant persons had slightly higher rates of injection-site pain and slightly lower rates of headache, myalgia, chills, and fever than nonpregnant women. Among the 827 pregnant persons who had a completed pregnancy reported in the V-safe pregnancy registry, the rates of adverse pregnancy and neonatal outcomes including pregnancy loss, preterm birth, small for gestational age, and congenital anomalies were similar to the published background rates; no neonatal deaths were reported.[47] Data from the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system administered by the CDC and the Food and Drug Administration (FDA), that collects information about the adverse events that occur after administration of a vaccine that may or may not be

TABLE
Safety data during pregnancy on COVID-19 vaccines authorized for use in the United States

Vaccine	Technology	Number of doses	Ages	Efficacy based on randomized clinical trials	Developmental and reproductive toxicity studies in animals	Safety signals in the general population (reporting rate of adverse outcomes and population with highest rate)	Published safety data on pregnant persons
Pfizer-BioNtech mRNA vaccine (BNT162b2)	mRNA– encodes stabilized spike, lipid nanoparticles	Two doses, 3 wk apart	≥12 y	95% against symptomatic COVID-19	No safety concerns—rats given the vaccine before mating and in pregnancy—no effects on female mating performance, fertility, embryo-fetal or postnatal survival, growth, physical or neurofunctional development[30,43]	Myocarditis—more often after 2nd dosage—reporting rate: 3.5 cases per 1,000,000 second doses; highest rate population: males aged 18–29 y; (mRNA vaccine analyzed together)[46]	No evidence of obvious safety signals among 3598 pregnant participants in V-safe pregnancy registry who received the mRNA vaccine, 827 with completed pregnancies (mRNA vaccines analyzed together)[47]; no evidence of adverse outcomes among 390 pregnant persons who received the Pfizer vaccine[48]; no evidence of adverse perinatal outcomes among pregnant persons who received Pfizer (n=110), Moderna (n=18), or Oxford Astra Zeneca (n=13) (vaccines analyzed together[49]); no evidence of increased risk of adverse perinatal outcomes among 13 pregnant persons who received the mRNA vaccine; type not specified[50]; no concerning trends in the perinatal outcome among 65 pregnant persons who received the Pfizer vaccine [a,b,51].

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(continued)

TABLE
Safety data during pregnancy on COVID-19 vaccines authorized for use in the United States *(continued)*

Vaccine	Technology	Number of doses	Ages	Efficacy based on randomized clinical trials	Developmental and reproductive toxicity studies in animals	Safety signals in the general population (reporting rate of adverse outcomes and population with highest rate)	Published safety data on pregnant persons
Moderna mRNA-1273 vaccine	mRNA, encodes stabilized spike, lipid nanoparticle	Two doses, 28 d apart	≥18 y	94.1% against symptomatic COVID-19	No safety concerns—rats were given vaccine before mating and during pregnancy—no adverse effects on female fertility, embryo-fetal or postnatal survival, growth, or development, except for skeletal variations which are common and resolve postnatally.[30,43]	Myocarditis – more often after second dosage—3.5 cases per 1,000,000 second doses—highest rate among males aged 18–29 y (mRNA vaccine analyzed together)[46]	No evidence of obvious safety signals among 3598 pregnant participants in V-safe pregnancy registry who received mRNA vaccine, 827 with completed pregnancies (mRNA vaccines analyzed together)[47]; no evidence of adverse perinatal outcomes among pregnant persons who received Pfizer (n=110), Moderna (n=18), or Oxford Astra Zeneca (n=13) (vaccines analyzed together[49]); No evidence of increased risk of adverse perinatal outcomes among 13 pregnant persons who received mRNA vaccine; type not specified[50]; no concerning trends in perinatal outcome among 20 pregnant persons who received Moderna vaccine [a,b 51].
Janssen Biotech, Inc (Johnson & Johnson) Ad26.COV2.S vaccine:	Replication-incompetent human adenovirus type 26 vector-stabilized spike	One dosage	≥18 y	66.1% against moderate to severe-critical COVID-19; 85.4% against severe-critical COVID-19	No safety concerns—female rabbits were given the vaccine before mating and during pregnancy—no vaccine-related adverse effects on female fertility, embryo-fetal or postnatal development up to postnatal day 28.[30,43]	Thrombosis with thrombocytopenia syndrome—3 cases per 1,000,000 doses administered—highest rate in females aged 30–49 y.[46] Guillain-Barre syndrome—7.8 cases per 1,000,000 doses administered – highest rate in males aged 50–64 y.[46]	We are not aware of published data on use of Janssen vaccine during pregnancy. No adverse pregnancy-related outcomes in clinical trials that used the same vaccine platform, including large Ebola vaccination trial[b].

[a] A preprint publication (not yet peer reviewed) reporting updated data from V-safe confirms that the receipt of an mRNA vaccine preconception or during pregnancy is not associated with an increased risk of spontaneous abortion[52]; [b] A preprint publication (not yet peer reviewed) reports no increased risk of a composite adverse outcome (including maternal death, uterine rupture, intensive care unit admission, return to the operating room, postpartum hemorrhage, perineal laceration, fetal or neonatal death, neonatal encephalopathy, low Apgar, neonatal intensive care unit admission, low birthweight, neonatal birth trauma) among pregnant persons who received Pfizer (n=127), Moderna (n=12), or Janssen (n=1) (vaccines analyzed together).[53]

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associated with vaccine administration, are also reassuring. In the first 2 months of vaccine administration, 221 adverse pregnancy events were reported to VAERS, including 46 spontaneous abortions, which was similar to what was observed with the 2009 H1N1 inactivated influenza vaccine.[47] However, the VAERS data are difficult to interpret, given that the total number of COVID-19 vaccine doses given during pregnancy is unknown. Healthcare providers should report any clinically significant adverse event to VAERS, regardless of whether the vaccine is known to be associated with the event.[58]

The safety data about the Johnson & Johnson—Janssen (adenoviral vector) COVID-19 vaccine are more limited, because it was authorized for use later, and far fewer vaccines have been administered. At the time of authorization, the data from the studies conducted on animals and on 4 pregnant persons who received the COVID-19 vaccine during clinical trials were reassuring; over 1500 pregnant persons had received an Ebola vaccine using the same adenoviral vector without adverse effects. The FDA concluded that the data were currently insufficient to make conclusions about the safety of the vaccine in pregnancy.[59] Although no safety signals have been detected in pregnancy, the safety data about all 3 currently available vaccines during pregnancy are limited. Additional information about the birth outcomes, particularly among the persons vaccinated earlier in pregnancy, are needed.

Following the issuance of the Johnson & Johnson—Janssen emergency use authorization by the FDA, 6 cases of cerebral venous sinus thrombosis with thrombocytopenia were reported among the vaccine recipients. Similar cases of thrombosis with thrombocytopenia syndrome (TTS) were reported after vaccination with the Oxford AstraZeneca adenoviral vaccine (United Kingdom, Sweden) that is available in multiple countries outside the United States[60]. After a 10-day pause in the use of the vaccine in the United States so that all the cases of TTS associated with vaccine use could be carefully reviewed, an additional 9 cases were identified. Most of the cases were in women aged 18 to 49 years, for a rate of 7.0 cases per 1 million Johnson & Johnson—Janssen COVID-19 vaccine doses given to women in this age group. After a careful review of the risks and benefits of COVID-19 vaccination, the CDC and the FDA reaffirmed its use in all persons $\geq$18 years and issued a warning that rare clotting events might occur after vaccination, particularly among women aged 18 to 49 years.[61] The clinicians should ensure that women younger than 50 years of age are aware of the risk of this rare adverse event and that other COVID-19 vaccines for which this risk has not been seen are available. Although the overall risk of thrombosis is increased during pregnancy and after childbirth, the mechanism of TTS is distinct from the pregnancy-associated thrombosis, and therefore, there is no specific concern for pregnant persons distinct from those who are not pregnant.[43] However, the United Kingdom preferentially recommends mRNA vaccines rather than adenoviral vaccines based on these safety concerns.[55]

In terms of vaccine effectiveness, studies indicate that the administration of the mRNA vaccines results in a robust maternal humoral response. Although the antibody response to vaccination among pregnant persons has not been rigorously compared with the response among nonpregnant persons, there is no reason to expect differences. Furthermore, maternal immunoglobulin G antibodies efficiently cross the placenta, resulting in relatively high titers in the fetus.[50,62—65] However, the degree to which these fetal antibody titers correlate with infant protection from SARS-CoV-2 infection is unknown.

Regarding the vaccination of lactating persons, there are no known or theoretical risks of vaccination. In general, there are no restrictions to the vaccination of lactating persons, and even live viral vaccines such as measles-mumps-rubella vaccines, which are contraindicated during pregnancy, are routinely given to unvaccinated persons postpartum. High titers of vaccine-induced antibodies against SARS-CoV-2 have been found in breastmilk.[50,64] However, whether this correlates with protection of the breastfed infant is unknown.

Several myths and misconceptions have arisen about the COVID-19 vaccines, and clinicians need to be prepared to respond to the questions regarding these patient concerns. Women should be reassured that there is no evidence that the COVID-19 vaccines affect fertility and that even in COVID-19 vaccine clinical trials, from which pregnant persons were excluded, several pregnancies occurred.[66] The patients should also be aware that these vaccines cannot cause COVID-19 as none of them contain the live virus, that the COVID-19 vaccines do not interact with or alter genetic material, and that the vaccines do not contain any controversial substances (eg, fetal cells or tracking devices). The CDC recommends that the clinicians listen and respond to the patient concerns regarding the COVID-19 vaccines with empathy.[67] As with other vaccines, discussion with a clinician is important; in a recent Kaiser Family Foundation poll, nearly 80% of respondents reported that they would be most likely to turn to their healthcare provider when deciding whether to get a COVID-19 vaccine.[68]

Conclusions

From the time of the reports of the first cases of COVID-19 in late 2019, much has been learned about the effects of SARS-CoV-2 infection during pregnancy. However, many questions remain. Pregnancy increases the risk of severe disease associated with COVID-19, but whether pregnant persons are more susceptible to infection is unknown. The intrauterine transmission of SARS-CoV-2 appears to be rare, and this is possibly related to low levels of SARS-CoV-2 viremia and a decreased coexpression of ACE2 and TMPRSS2 needed for SARS-CoV-2 entry into the cells in the placenta. Adverse pregnancy and neonatal outcomes are more common among the persons infected with SARS-CoV-2 during pregnancy, especially among those with severe disease.

Although pregnant and lactating persons were excluded from the initial clinical trials that led to the authorization of 3 COVID-19 vaccines in the United States, no concerns have arisen about safety, despite the large numbers of pregnant and lactating persons vaccinated. Despite reports of rare clotting events in vaccinated persons, there is no particular concern for those with a prothrombotic state, including pregnancy. In addition, the available data suggest that vaccination during pregnancy is associated with the transmission of SARS-CoV-2 antibodies to the fetus. The vaccination of lactating persons is associated with high levels of SARS-CoV-2 antibodies in the breast milk. However, the level of protection to the infant that is provided by transplacental antibodies and by those found in breastmilk is unknown. The data on vaccine coverage suggest that pregnant persons are less likely to receive a COVID-19 vaccine despite their increased risk for severe disease and the risks of adverse pregnancy and neonatal outcomes if infected.

Most experts believe that SARS-CoV-2 is likely to become endemic.[69] Thus, the continued collection of data on the effects of SARS-CoV-2 infection during pregnancy and the effects of COVID-19 vaccines are needed. In addition, given the increasing connectedness of the world's population, climate change, and the increasing encroachment of human populations on wildlife habitats, the emergence of another infection with global effects is likely.[70] Therefore, it is essential that we maximize the lessons learned from the COVID-19 pandemic so that they can be applied to improve our planning for and response to emerging infections in the future. ■

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