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COVID-19 and Pregnancy



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KEYWORDS

- Pregnancy • COVID-19 • SARS-CoV-2 vaccine • Intrauterine transmission
- SARS-CoV-2 • Pregnancy complications • mRNA vaccine

KEY POINTS

- Pregnant persons are at increased risk for severe disease from COVID-19.
- SARS-CoV-2 crosses the placenta rarely, but adverse effects of maternal disease on the fetus and newborn have been observed.
- Studies show that SARS-CoV-2 vaccines during pregnancy are effective at preventing disease in the mother and safe for both the mother and the fetus. Antibodies to SARS-CoV-2 have been found in umbilical cord blood and breast milk following vaccination during pregnancy, suggesting protection of the infant after maternal vaccination.

INTRODUCTION

Since the emergence of SARS-CoV-2 in late 2019, the virus and the response to it have had catastrophic effects on the world's health, societies, and economies. Early on, data on the effects of SARS-CoV-2 on the pregnant person and fetus were limited. Data on the effects during pregnancy of previous coronaviruses (severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) are sparse, but those data along with information on other respiratory infections such as influenza raised concerns about the potential effects of COVID-19 during pregnancy.¹ Here we review available information on the effects of SARS-CoV-2 infection during pregnancy and the effectiveness and safety of the SARS-CoV-2 vaccines in protecting pregnant persons and their newborns from COVID-19.

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EFFECTS OF SARS-CoV-2 INFECTION DURING PREGNANCY

An initial question after emergence of a novel pathogen is whether pregnancy is a risk factor for infection or severe disease. Successful pregnancy requires changes in the pregnant person's immune system to tolerate a genetically foreign fetus. These changes in the immune system as well as alterations in the cardiac, pulmonary, and other systems can result in increased susceptibility to or increased morbidity and mortality with infection during pregnancy.² Understanding the susceptibility to infection during pregnancy is challenging, given that the number of infections observed depends not only on susceptibility but also on the level of exposure to the pathogen. Pregnant persons might be more cautious about risk, resulting in a lower level of exposure, which could seem as decreased susceptibility. To adequately address this question, a comparison of incident rates between pregnant persons and women of the same age with similar levels of SARS-CoV-2 exposure would be needed. A prospective cohort analysis of incident disease among pregnant persons identified through weekly self-collected testing showed an incidence during pregnancy that was similar to the modeled estimates for US adults of reproductive age during the same time period.³ Thus, currently available data do not support increased susceptibility to SARS-CoV-2 infection during pregnancy,⁴ but conclusions are difficult, given issues with potential differences in exposure levels between pregnant and nonpregnant persons.

Studies to determine whether pregnancy increases the risk for severe disease are also challenging, given the increased surveillance and enhanced clinical response to illness that occur during pregnancy, as well as potential confounding factors (eg, pregnancy being a marker of better health).⁵ Several early studies did not include appropriate comparison groups; however, later studies that have compared pregnant persons with nonpregnant women of reproductive age have suggested that pregnancy is a risk factor for severe disease.⁴ A systematic review and meta-analysis showed increased odds of admission to an intensive care unit (ICU) (odds ratio [OR] 2.13, 95% confidence interval [CI] 1.53–2.95, 7 studies, $n = 601,108$), of invasive ventilation (OR 2.59, 95% CI 2.28–2.94, 6 studies, $n = 601,044$), and of the need for extracorporeal membrane oxygenation (ECMO) (OR 2.02, 95% CI 1.22–3.34, 2 studies, $n = 461,936$) for pregnant and recently pregnant persons compared with nonpregnant women of reproductive age.⁶ These findings are similar to those in a study from the Centers for Disease Control and Prevention (CDC) of more than 400,000 women of reproductive age with symptomatic COVID-19, which also showed a significantly elevated adjusted risk ratio (aRR) for death among pregnant persons (aRR = 1.7, 95% CI 1.2–2.4), compared with nonpregnant women of reproductive age; however, pregnancy status was missing in more than half of reported cases.⁷ A study from Colombia also showed a significantly increased risk of death among pregnant persons, compared with nonpregnant women of reproductive age (aRR = 1.82, 95% CI 1.60–2.07, $n = 371,363$).⁸ Several risk factors for severe disease during pregnancy have been identified, including higher maternal age, high body mass index, nonwhite ethnicity, and prepregnancy comorbid conditions, such as diabetes and hypertension.⁴

Studies of COVID-19 suggest that the postpartum period is also one of increased risk, similar to what was seen with 2009 H1N1 influenza.⁹ For example, analysis of a prospective cohort from New York City showed a high risk of severe disease during the postpartum period; among patients with an asymptomatic presentation during pregnancy, clinical worsening or new symptoms occurred during the first 7 days after birth in 13% of women.¹⁰ The risk for postpartum complications (eg, fever, hypoxia, or

need for readmission) was higher among patients with COVID-19 (12.9%) compared with those without COVID-19 (4.5%, $P < .001$).¹⁰ In a multivariate analysis in Brazil that compared nonpregnant SARS-CoV-2-infected women with those who were pregnant or postpartum (defined as up to 42 days after childbirth), the postpartum period was associated with the highest odds for death (OR = 1.90, 95% CI 1.53–2.35). Among those who were postpartum, age greater than 35 years and diabetes were independently associated with increased risk of death. Postpartum status was also associated with an increased rate of ICU admission and invasive ventilation.¹¹

Because SARS-CoV-2 testing is often performed as part of screening for hospital admission at delivery, pregnant and recently pregnant persons who test positive for SARS-CoV-2 infection are less likely to report symptoms (OR 0.28, 95% CI 0.13–0.62).⁶ In a prospective cohort of individuals tested weekly for SARS-CoV-2, 99 participants tested positive, with 20 (20%) reporting no symptoms throughout their infections. Among those with detailed symptom data, nasal congestion (72%), cough (64%), headache (59%), and changes in taste or smell (54%) were most commonly reported; a measured or subjective fever was reported in 28%.³

TREATMENT OF COVID-19 DURING PREGNANCY

The National Institutes of Health has developed treatment guidelines for care of patients with COVID-19, which are updated regularly (<https://www.covid19treatmentguidelines.nih.gov/>). Many clinical trials evaluating novel treatments for COVID-19 have excluded pregnant persons; however, treatment recommended for the nonpregnant population should not be withheld from pregnant persons; this includes treatment with remdesivir, dexamethasone, and monoclonal antibodies. Given that pregnancy is a risk factor for progression to serious disease, pregnant persons are eligible to receive outpatient treatment or postexposure prophylaxis with anti-SARS-CoV-2 monoclonal antibodies under the Emergency Use Authorization.^{4,12}

Clinical algorithms for care of pregnant and nonpregnant patients with COVID-19 are generally similar; however, use of algorithms specific to pregnancy can account for some important differences. For example, peripheral oxygen saturation during pregnancy should be maintained at 95% or greater to ensure a favorable oxygen diffusion gradient across the placenta.¹³ Timing of delivery for pregnant patients needs to be individualized, weighing the benefits and the risks to the patient and fetus.¹³ In the setting of a patient with refractory hypoxemia at or after 32 weeks gestation or in the setting of worsening or persistent critical illness, it is reasonable to consider delivery. In a recent study of pregnant patients with COVID-19–related acute respiratory distress syndrome (ARDS), delivery resulted in a small improvement of P_{O_2}/F_{iO_2} ratio, an indicator of ARDS severity.¹⁴ However, the investigators emphasized that this study was not generalizable to patients without ARDS who are at significantly lower morbidity and mortality risk.

EFFECTS OF SARS-CoV-2 ON PREGNANCY OUTCOMES

Several studies have shown that SARS-CoV-2 infection during pregnancy increases the risk of pregnancy complications. In a systematic review and meta-analysis that included 42 studies of 438,548 pregnant persons, COVID-19 was associated with an increased risk for preeclampsia, preterm birth, and stillbirth, compared with no SARS-CoV-2 infection during pregnancy. Severe COVID-19 disease (defined as presence of dyspnea, respiratory rate of ≥ 30 breaths per minute and an oxygen saturation of 93% or less on room air, or findings consistent with pneumonia) was strongly associated with preeclampsia, gestational diabetes, cesarean delivery, preterm birth, low

birth weight, and admission to the neonatal intensive care unit, compared with mild disease (defined as a positive test for SARS-CoV-2 without severe symptoms).¹⁵ In a large study using data from 499 US academic health centers or community affiliates published after the systematic review, COVID-19 diagnosis was not associated with an increased risk of cesarean delivery ($P = .57$); however, the association between diagnosis of COVID-19 and preterm birth remained ($P < .001$).¹⁶ A systematic review and meta-analysis focusing on the effects of SARS-CoV-2 infection during pregnancy and preeclampsia showed increased odds for preeclampsia; preeclampsia with severe features; eclampsia; and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome among pregnant persons with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection. Increased odds of preeclampsia were seen in patients with both asymptomatic and symptomatic SARS-CoV-2 infection; however, the odds were higher among symptomatic patients.¹⁷ In a recent study of nearly 500,000 hospitalizations in 703 US hospitals, pregnant persons with a documented COVID-19 diagnosis were only slightly more likely to have a cesarean delivery (33.5 vs 32.0%, $P = .0093$) and preterm labor with a preterm delivery (aRR 1.2, 95% CI 1.1–1.3) than those without a COVID-19 diagnosis. The investigators noted that differences in the risks of cesarean delivery and preterm birth might be related to different obstetric intervention practices across populations and geographic areas.¹⁸

INTRAUTERINE TRANSMISSION OF SARS-CoV-2

When a newborn infant tests positive for SARS-CoV-2, it can be difficult to determine whether transmission was intrauterine (during pregnancy and before labor onset), intrapartum (during labor and delivery), or postnatal, either through contact with the mother or others or through breastfeeding. Criteria to evaluate whether intrauterine transmission has occurred have been developed and include documentation of maternal infection, identification of SARS-CoV-2 in the first 24 hours of life, and evidence of persistence of infection in the neonate.^{19–21} Although intrauterine transmission of SARS-CoV-2 has been documented,²² it seems to be rare. In a systematic review that included 1141 neonates born to infected pregnant persons, 58 newborns had documented SARS-CoV-2 infection; 4 of these were believed to be congenital (2 confirmed, 1 probable, and 1 “not sure”), 41 were acquired postpartum, and 13 were unclassified because of missing information.²³ The reasons for the low frequency of intrauterine transmission of SARS-CoV-2 are not fully understood but might be related to low levels of viremia with SARS-CoV-2 infection²⁴ and the lack of placental coexpression of factors that facilitate SARS-CoV-2 entry into cells (ie, angiotensin-converting enzyme 2 and transmembrane serine protease 2),^{25,26} although not all studies have been consistent on this issue.²⁷

A recent study has suggested that the placental immune response to SARS-CoV-2 infection differs depending on the sex of the fetus. When the fetus was male, maternal SARS-CoV-2 antibody titers were lower, and antibody transfer across the placenta was impaired.²⁸ Whether these differences result in increased vulnerability of male infants to early life SARS-CoV-2 infection is unknown.

SARS-CoV-2 VACCINES AND PREGNANCY

Three vaccines have received emergency use authorization or full approval in the United States by the Food and Drug Administration (FDA): 2 messenger RNA (mRNA) vaccines (made by Pfizer/BioNTech and Moderna) and one viral vector vaccine made by Janssen (Johnson and Johnson). The clinical trials for these vaccines excluded pregnant persons. However, given the data on safety of other vaccines

during pregnancy and the known increased risk to pregnant persons of serious disease from COVID-19, CDC, American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) all made initial recommendations to ensure that pregnant persons could choose to be vaccinated.²⁹ Since that time, information has become available on the effectiveness and safety of the SARS-CoV-2 vaccines during pregnancy, leading ACOG and SMFM to change to a strong recommendation for vaccination during pregnancy on July 30, 2021, followed by CDC on August 11, 2021. After a record number of 22 deaths among pregnant persons in the United States in the month of August 2021 alone, CDC issued an urgent public health advisory on September 29, 2021, urging people who are pregnant, recently pregnant, or who might become pregnant in the future to get vaccinated.³⁰

In 2021, the FDA also authorized booster doses of all 3 available vaccines for certain populations (boosters for Pfizer/BioNTech were authorized on September 22 and boosters for Moderna and Johnson and Johnson vaccines were authorized on October 20, 2021). Booster doses are recommended for all persons 12 years and older, including pregnant persons, at least 5 months after the second dose of the Pfizer/BioNTech and Moderna vaccines, and at least 2 months after the first dose of the Janssen vaccine.

SARS-CoV-2 Vaccine Effectiveness During Pregnancy

With regard to effectiveness, antibody responses during pregnancy were found to have similar immunogenicity and reactogenicity to those in nonpregnant women.^{31,32} The second dose of the vaccine was essential for pregnant persons to achieve adequate immune responses similar to those of nonpregnant women.³³ An analysis of responses against the B.1.1.7 (Alpha) and B.1.351 (Beta) variants of concern showed reduced antibody titers, but preserved T-cell responses.³⁴ In addition, vaccine-generated antibodies during pregnancy were found to be significantly higher than those induced by SARS-CoV-2 infection during pregnancy.³¹ In a large retrospective cohort study from Israel, the likelihood of infection in vaccinated versus unvaccinated pregnant persons suggested significant protection from the vaccine (adjusted hazard ratio of 0.22 [95% CI 0.11–0.43]).³⁵ Vaccine effectiveness after the second dose of vaccine during pregnancy was found to be similar to that seen in the general population: 96% (95% CI 89%–100%) for any documented infection, 97% (95% CI 91%–100%) for symptomatic infection, and 89% (95% CI 43%–100%) for COVID-19-associated hospitalization against alpha and ancestral variants.³⁶

SARS-CoV-2 Vaccine Safety During Pregnancy

Safety data on mRNA vaccine-exposed pregnancies from 3 vaccine safety systems in the United States have been reassuring. Pregnant persons were less likely to report headache, myalgia, chills, and fever and more likely to report pain at the injection site. The frequencies of adverse pregnancy and neonatal outcomes were similar to those seen in studies before the COVID-19 pandemic, suggesting no increase in adverse outcomes related to vaccination.³⁷ Similar findings were seen in studies from Israel. A study of more than 500 pregnant persons who were vaccinated throughout pregnancy showed no increase in the rate of obstetric complications.³⁸ In a study of more than 700 pregnant persons vaccinated in the third trimester of pregnancy, adverse maternal outcomes were not increased; however, those who were vaccinated had a higher rate of elective cesarean delivery and a lower rate of vacuum-assisted vaginal delivery. A composite score for adverse neonatal outcomes showed a lower risk among those vaccinated compared with unvaccinated.³⁹ Three

studies have specifically addressed the risk of pregnancy loss after receiving the SARS-CoV-2 vaccine and have found no increased risk. These included data from a CDC COVID-19 vaccine pregnancy registry,⁴⁰ a case-control analysis from 8 health systems in the United States,⁴¹ and a case-control study using several Norwegian national health registries.⁴² These studies primarily focused on the use of mRNA vaccines, although a small proportion of pregnancies in the study from Norway were exposed to the ChAdOx1-S/nCoV-19 (recombinant) vaccine.

SARS-CoV-2 Vaccines During Pregnancy and Protection of the Infant

Other vaccines (ie, inactivated influenza and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) are recommended during pregnancy because of their ability to protect infants from influenza and pertussis, respectively, during the first few months of life. Therefore, another important question is whether SARS-CoV-2 vaccine during pregnancy provides immune protection to the infant. SARS-CoV-2 antibodies were seen in umbilical cord blood and breast milk after vaccination with mRNA vaccines during pregnancy in several studies, suggesting that maternal vaccination might provide some protection to the infant.^{31,34,43–45} In one study, infants whose mothers had a longer time period between vaccination and delivery and who had received both doses of the vaccine had higher levels of immunoglobulin G (IgG) antibodies. In 3 infants (one set of twins) who did not have IgG in umbilical cord blood, mothers were vaccinated less than 3 weeks before delivery.⁴³ In another study, IgG antibodies were detected in maternal and umbilical cord blood samples of all pregnancies by 4 weeks after the vaccine dose, except for one. IgG was detectable in 44% and 99% of cord blood samples in which the pregnant person had received only 1 vaccine dose and 2 doses of vaccine, respectively,⁴⁶ again emphasizing the importance of pregnant persons receiving the full vaccine series.

SARS-CoV-2 Vaccine Hesitancy During Pregnancy

Despite the availability of reassuring data on effectiveness and safety of the SARS-CoV-2 vaccines, the uptake of SARS-CoV-2 vaccines has been lower than that of the general population. As of October 23, 2021, less than 35% of pregnant people in the United States reported being fully vaccinated for COVID-19 before or during pregnancy. Rates varied by race and ethnicity, ranging from the highest rate in non-Hispanic Asians (49.8%) to the lowest rate in non-Hispanic Black persons (19.2%).⁴⁷ In a study of vaccine uptake among health care workers in a medical center in Israel during the first months after vaccine roll-out, the most common reason for declining the vaccine was concerns about risks during pregnancy.⁴⁸

Other studies have identified factors associated with the likelihood of receiving COVID-19 vaccination during pregnancy. In an analysis of pregnant patients in Israel, those who received both doses of the vaccine were likely to be older and to have had previous miscarriages, previous cesarean deliveries, or fertility treatments.³⁹ In a study of persons giving birth at a hospital in the United Kingdom, lower vaccine uptake was seen among younger persons, persons of lower socioeconomic background, and people not identified as White. Higher vaccine uptake was seen in pregnant persons with prepregnancy diabetes.⁴⁹

In a survey of pregnant persons in Italy, 28.2% agreed to be vaccinated. Most noted that pregnancy influenced their decision, even though the majority (90.1%) reported being generally in favor of vaccines. The main reason for declining the vaccine was fear of the effects on their baby's health.⁵⁰ In a study from Germany conducted between March 30 and April 19, 2021, most (57.4%) of the pregnant respondents were not in favor of receiving the vaccine, 28.8% were unsure, and only 13.8% would

get vaccinated. Nearly half (47.2%) of the pregnant respondents were in favor of receiving the vaccine if more scientific evidence on vaccine safety were available. The main reasons for vaccine hesitancy were concerns about limited information about the vaccine, limited information on vaccine safety, and fear of harm to the fetus or infant. When asked who the best contact person would be for questions regarding COVID-19 vaccination, pregnant persons named their gynecologist.⁵¹

A study conducted at a single academic health center in Missouri from April 27 to May 20, 2021 addressed whether improving vaccine access would result in increased SARS-CoV-2 vaccine uptake by comparing time periods when SARS-CoV-2 vaccines were available onsite versus before onsite vaccine availability. No difference in vaccine uptake was noted during these time periods, suggesting that vaccine hesitancy, not convenience, was the critical issue causing low vaccination rates in their population.⁵²

Shook and colleagues⁵³ recently proposed a framework to address vaccine hesitancy during pregnancy. Their framework included addressing the “four Cs”: confidence, complacency, convenience, and compassion. Increasing vaccine confidence by addressing concerns about safety, combatting complacency due to the perception that a pregnant person is at low-risk, increasing vaccine convenience by offering the vaccine at the time of a prenatal appointment, and the need for compassionate conversations between obstetric care providers and vaccine-hesitant pregnant persons are all believed to be important to increase vaccination rates among this population.

One reason frequently cited for declining COVID-19 vaccination has been concerns about fertility. The issue regarding female fertility initially arose from a blog post that noted a similarity between the spike protein of SARS-CoV-2 and a protein on the placenta, syncytin-1, with a hypothesis that vaccine-induced antibodies could target the placental protein and result in infertility. Although the similarity between the 2 proteins is minimal and no evidence for infertility had been seen among women following COVID-19 infection, who also would have exposure to antibodies to the spike protein, this false information spread quickly. Several pieces of information can be used to address this rumor. First, convalescent serum from patients with COVID-19 does not react with syncytin-1 protein. Second, no evidence of fertility issues was seen in the developmental and reproductive toxicology studies done on animals before vaccine authorization. Third, despite pregnant people being excluded from the clinical trials and participants being asked to avoid pregnancy, 57 pregnancies occurred, with similar numbers of inadvertent pregnancies in the vaccinated and placebo groups. Finally, no increases in rates of miscarriage have been seen following vaccination in pregnancy, a finding that might be expected if antibodies were causing damage to the placenta.⁵⁴ More recently, concerns, again unfounded, have been raised about male infertility. Studies have shown no decreases in any sperm parameters after receipt of a COVID-19 mRNA vaccine.⁵⁵ Thus, based on available data, there is no evidence to support any negative effects on female or male fertility related to SARS-CoV-2 vaccines.

SUMMARY

Pregnant persons are at increased risk for severe disease during pregnancy, with increased risk of admission to an ICU, increased need for mechanical ventilation, need for ECMO, and likely increased risk of death. In general, treatment of COVID-19 during pregnancy is similar to nonpregnant persons, with a few modifications. Treatment should not be withheld based on pregnancy status, but rather pregnant persons should be prioritized for early treatments such as antivirals and monoclonal

antibodies to prevent severe outcomes. Intrauterine transmission of SARS-CoV-2 occurs but is rare, possibly related to the low rate of SARS-CoV-2 viremia and an absence of coexpression of receptors on the placenta that facilitate SARS-CoV-2's entry into cells. However, even in the absence of intrauterine transmission, SARS-CoV-2 infection during pregnancy increases the risk of adverse pregnancy outcomes, especially among those severely affected. Available data on SARS-CoV-2 vaccines during pregnancy suggest that they are safe and effective. In addition, SARS-CoV-2 antibodies have been identified in umbilical cord blood and in breast milk following vaccination during pregnancy, suggesting that maternal vaccination provides some degree of protection to the infant. However, coverage rates among pregnant persons remain low as of late 2021; available data suggest that concerns regarding the safety of the vaccine on the fetus are key to vaccine hesitancy during pregnancy. Additional studies are needed to better understand ways to address vaccine hesitancy among pregnant persons.

CLINICS CARE POINTS

- Effective COVID-19 treatments such as remdesivir, dexamethasone, and monoclonal antibodies should not be withheld from pregnant persons. Pregnancy is a high-risk condition, which is considered a priority indication for early treatment or prophylaxis with SARS-CoV-2 monoclonal antibodies and antivirals.
- Because COVID-19 is associated with an increased risk of poor pregnancy outcomes such as preeclampsia, preterm birth, and stillbirth, pregnant persons with COVID-19 infection should be closely monitored, particularly those with severe disease.
- Health care providers should emphasize to their pregnant patients the importance of being fully vaccinated for COVID-19 and of receiving booster doses of vaccine.

DISCLOSURES

None.

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