Open Forum Infectious Diseases

REVIEW ARTICLE

SARS-CoV-2 Vaccination During Pregnancy: A Complex Decision

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As the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines passed UK and US regulatory milestones in late 2020 and early 2021, multiple professional societies offered recommendations to assist pregnant and breastfeeding people as they choose whether to undergo vaccination. Despite such guidance, the lack of data describing vaccine safety, immunogenicity, and efficacy in pregnant and breastfeeding people has made this decision challenging for many. However, even considering the paucity of data, the known risks of coronavirus disease 2019 during pregnancy likely outweigh the not yet fully elucidated risks of SARS-CoV-2 vaccines, which have reassuring safety and efficacy profiles among nonpregnant people.

Keywords. breastfeeding; COVID-19; pregnancy; SARS-CoV-2; vaccine.

Essential workers and high-risk individuals in the United Kingdom and the United States began receiving doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines en masse as the first vaccine candidates obtained Emergency Use Authorization in December 2020. While the safety, immunogenicity, and efficacy data for the 4 authorized vaccines are reassuring so far [1–4], none of these vaccines has been systematically studied in pregnant and breastfeeding people, despite evidence that pregnancy may increase the risk of developing severe coronavirus disease 2019 (COVID-19) and related complications. In the United States, ~10% of pregnant people with COVID-19 have severe or critical illness [5, 6], and their in-hospital mortality is significantly higher compared with nonpregnant people of similar age [7]. The decision of whether to undergo SARS-CoV-2 vaccination during pregnancy is complex and causes apprehension among those considering vaccination [8]. Here, we discuss the risks and benefits of SARS-CoV-2 vaccination in pregnancy that may influence the decision-making process.

RISK OF PREGNANCY COMPLICATIONS DUE TO SARS-COV-2 INFECTION

It is unclear whether pregnant people are more susceptible to SARS-CoV-2 infection than nonpregnant people. Many pregnant people infected with SARS-CoV-2 are asymptomatic (ranging from 44% to 86% in cohort studies with universally tested pregnant populations [9–11]). While the risk of mortality is low and comparable to that of the nonpregnant population (0.1%–0.2%), preexisting comorbidities, higher maternal age, and higher body mass index are risk factors for severe COVID-19 in pregnancy [12–15]. Pregnant people who develop COVID-19 are more likely to require intensive care and to have severe cardiopulmonary complications than their nonpregnant counterparts [13, 15, 16] (though these studies had several limitations; for instance, in the US Centers for Disease and Prevention [CDC] reports, pregnancy status and information on symptoms and underlying conditions were missing from >50% of cases [13, 15]). One retrospective evaluation of a large US cohort of hospitalized pregnant patients found that in-hospital mortality was significantly higher in those with COVID-19 compared with those without COVID-19 (141; 95% CI, 65–268; vs 5.0; 95% CI, 3.1–7.7; deaths per 100 000 women) [7]. Additionally, some studies have suggested that pregnant people with COVID-19 have an increased risk of delivering premature and/or low-birthweight infants, of postpartum hemorrhage, and of complications requiring cesarean delivery [10, 11, 17–19]. Vertical transmission of SARS-CoV-2 certainly occurs (both in utero, which is uncommon, and peripartum), though infected infants tend to have asymptomatic disease or only mild symptoms [20, 21]. Furthermore, pregnant people who develop COVID-19 in low-resource settings—where pregnancy outcomes are already poorer due to prevalent comorbidities, coinfections, and socioeconomic and health system inequalities—often lack access to effective medications and high levels of supportive care [22, 23].

Received 15 January 2021; editorial decision 5 April 2021; accepted 8 April 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab180

EXCLUSION OF PREGNANT PEOPLE FROM SARS-COV-2 VACCINE TRIALS HAS RESULTED IN LIMITED DATA DESCRIBING VACCINE SAFETY AND EFFICACY IN PREGNANCY

Exclusion of pregnant people from vaccine trials has been an longstanding problem [24]. Their exclusion has resulted in vaccine recommendations for pregnant women based on little data (eg, as for the initial recommendations for inactivated influenza vaccines [25], though subsequently robust clinical trials supported these recommendations) or recommendations only being given once "enough" pregnant people have been inadvertently vaccinated (eg, as for MenAfriVac, a meningococcal A conjugate vaccine [26]). Since 2018, both governmental and independent advisory groups have published recommendations advocating for the early inclusion of pregnant people in the development and deployment of vaccines against emerging pathogens [27, 28]. Subsequently, during the rapid emergence of SARS-CoV-2, many authorities advocated for inclusion of pregnant people in SARS-CoV-2 vaccine trials [29, 30]. Despite this expert guidance and the potentially devastating consequences of SARS-CoV-2 infection, pregnant people were explicitly excluded from SARS-CoV-2 vaccine clinical trials. Consequently, to date there are few published data describing the safety or efficacy of any SARS-CoV-2 vaccine in human pregnancy.

SARS-COV-2 VACCINE PLATFORMS AUTHORIZED IN THE UK AND US AND THEIR POTENTIAL RISKS

Historically, protein-based vaccines (which are nonreplicating) have been considered safe in pregnancy for both mother and fetus. In fact, the CDC's Advisory Committee on Immunization Practices (ACIP) recommends routine influenza and Tdap vaccination of all pregnant women as these vaccines are safe and induce maternal antibodies that are passed to the child in utero and via breastfeeding, thereby protecting the child from the diseases targeted by these vaccines [31]. As of March 15, 2021, 4 SARS-CoV-2 vaccines have gained regulatory authorization either in the United Kingdom or the United States, including the Pfizer/BioNTech, Moderna/National Institutes of Health (NIH), Oxford/AstraZeneca, and Janssen vaccines. While all 4 authorized SARS-CoV-2 vaccines are nonreplicating vaccines, they are based on relatively new vaccine technology. Both the Pfizer/BioNTech and Moderna/NIH vaccines are messenger RNA (mRNA) nanoparticle-based platforms encoding the SARS-CoV-2 spike protein that require 2 doses spaced 3 to 4 weeks apart [32, 33]. The Oxford/AstraZeneca and Janssen vaccines are replication-deficient adenovirus vector vaccines containing spike protein DNA [34, 35]. The Oxford/AstraZeneca vaccine also requires 2 doses, while the Janssen vaccine is authorized for use as a single-dose vaccine. In contrast to conventional protein-based vaccines, these nucleic acid–based vaccines provide genetic blueprints that allow the recipient's own cells to produce the target antigen. Theoretical concerns have been suggested regarding the potential for host genome insertion and mutagenesis of vaccine genetic material. However, these concerns are unsubstantiated by scientific evidence; the SARS-CoV-2 genetic material carried by these vaccines is not infectious, does not incorporate into the recipient's genome, and levels of vaccine mRNA/DNA and associated protein decline over several days postvaccination as they are degraded by normal host cellular processes [36, 37]. Research on nanoparticle and adenovirus-vectored vaccines has been ongoing for decades [36, 37]. Specifically, human adenovirus serotype 26 (Ad26; which is the Janssen vaccine vector) has been used as a vector for other vaccines deemed safe for the general public, including the Ad26.ZEBOV/MVA-BN-Filo Ebola vaccine that was approved in Europe in 2020, as well as investigational vaccines against Zika, filovirus, HIV, human papillomavirus, malaria, and respiratory syncytial virus. No adverse pregnancy outcomes have been reported for these vaccines. However, the current COVID-19 pandemic era is the first time that these vaccine types are being widely distributed among the general population.

Though pregnant individuals were excluded from initial clinical trials of the 4 vaccines authorized to date, these trials do provide information on adverse effects unrelated to pregnancy, which are important for pregnant people to consider before vaccination. In these trials, reports of serious adverse effects were rare (most notably, 3 cases of transverse myelitis were reported during the AstraZeneca/Oxford vaccine clinical trials but were thought unlikely to be related to the vaccine after independent safety committee review [38]). Short-lived, mild to moderate adverse reactions are common after vaccination with all 4 of the SARS-CoV-2 vaccines discussed here. For the mRNA vaccines, the most common adverse reactions were injection site reactions (84.1% for the Pfizer/BioNTech vaccine, 91.6% for the Moderna/NIH vaccine), fatigue (62.9%, 68.5%), headache (55.1%, 63.0%), muscle pain (38.3%, 59.6%), chills (31.9%, 43.4%), joint pain (23.6%, 44.8%), and fever (14.2%, 14.8%) [32, 33]. Local injection site reactions, fatigue, headache, fever, and muscle pains also were common for the Oxford/AstraZeneca [34] and Janssen vaccines (for which the most common adverse reactions were injection site pain [48.6%], headache [38.9%], fatigue [38.2%], and myalgia [33.2%] [35]).

Postclinical trial, "real-world" adverse effect analyses are ongoing, and have revealed some concern for thrombotic disease with use of the Janssen and Oxford/AstaZeneca vaccines. Use of the Janssen vaccine was temporarily paused in the US in April 2020 after several cases of thrombosis with thrombocytopenia syndrome were noted in reproductive age women. The CDC's ACIP reviewed available data and subsequently advised that, while the Janssen vaccine's benefits outweigh risks, women younger than 50 years old should be counseled about this risk in particular when evaluating their vaccine options. The Oxford/AstraZeneca vaccine also may carry a somewhat increased risk of thrombotic disease.

Whether such adverse effects are associated with any risks to the mother or fetus is unclear. Of the 4 vaccines discussed here, Pfizer/BioNTech, Moderna/NIH, and Janssen have completed preclinical developmental and reproductive toxicity (DART) studies; none found any adverse effects on animal reproduction or fetal development. Regarding human data, small numbers of pregnant people were inadvertently enrolled during vaccine clinical trials (23, including 12 in the vaccine arm, for the Pfizer/BioNTech vaccine [32]; 13, including 6 in the vaccine arm, for the Moderna/NIH vaccine [33]; and 8, including 4 in the vaccine arm, for the Janssen vaccine [35]). Oxford/AstraZeneca has not yet publicly disclosed information on whether pregnancies were reported during their clinical trials.

ONGOING AND PLANNED SARS-COV-2 VACCINE EVALUATIONS IN PREGNANT POPULATIONS

Though the small numbers of pregnant people discussed above were inadvertently enrolled in the SARS-CoV-2 vaccine clinical trials, the information generated by their follow-up is unlikely to provide conclusive evidence regarding vaccine safety or efficacy. Because pregnancy poses unique safety concerns, it is essential that pregnant people be included in appropriately designed vaccine trials. Pfizer recently announced that they will perform a global phase 2/3 trial to evaluate the safety, tolerability, and immunogenicity of the SARS-CoV-2 vaccine in pregnant people who are age 18 years and older [39]. The trial is a randomized, placebo-controlled, observer-blind study of 4000 healthy women vaccinated between 24 to 34 weeks of gestation. Each woman will participate in the study for 7–10 months, depending on whether randomized to receive vaccine or placebo, and their infants will be monitored to 6 months of age. Moderna has created a registry of pregnant vaccinees and is planning a prospective observational study to assess obstetric, neonatal, and infant outcomes [40]. Janssen is planning a phase 2 placebo-controlled trial in more than 800 pregnant people [41]. AstraZeneca's plans for clinical trials in pregnant people are still uncertain. It is important that these trials move forward to evaluate the remaining unknown issues related to pregnancy such as vaccine safety and immunogenicity (including rates of antibody transfer to neonates). However, potential problems with this delayed approach to inclusion of pregnant people in vaccine clinical trials include: (1) data are unavailable for pregnant people otherwise eligible for vaccination now, obligating reliance on observational data; (2) potential low trial enrollment if pregnant people do not want to risk being in the placebo arm; and (3) the resultant trial sample size may be too small to detect differences in perinatal outcomes.

Additionally, the CDC has established a voluntary smartphone-based registry for SARS-CoV-2 vaccine recipients called "v-safe," which includes both a postvaccination "health checker" and a registry of pregnant people; as of March 15, 2021, more than 50 000 pregnant people were enrolled in this monitoring program [42]. So far, v-safe data indicate no safety issues. Most adverse events (73%) reported were not related to pregnancy. Of the pregnancy-related adverse events, miscarriage was reported most frequently (in 29 participants); however, the reported miscarriage numbers reflect background rates [43]. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has a similar postvaccination registry and also found no safety concerns in pregnant people during their data analysis [44].

PUBLIC HEALTH AND PERSONAL ADVANTAGES OF SARS-COV-2 VACCINATION OF PREGNANT AND BREASTFEEDING PEOPLE

The obvious advantage of SARS-CoV-2 vaccination is protection of pregnant people—and, to some extent, their neonates—from the potentially devastating complications of SARS-CoV-2 infection. In nonpregnant populations, the efficacies reported for the authorized SARS-CoV-2 vaccines are 95.0% for the Pfizer/BioNTech vaccine [32], 94.1% for the Moderna/NIH vaccine [33], 70.4% for the Oxford/AstraZeneca vaccine (notably, this percentage is derived from pooled analysis of groups that received different vaccine doses [38]), and 66.9% for the Janssen vaccine [35]. Efficacies are likely to be similarly robust in pregnant populations. Prospective studies have already described SARS-CoV-2 vaccine-induced immune responses in pregnant and lactating people, with even higher antibody titers than those induced by SARS-CoV-2 infection during pregnancy [45]. From a public health perspective, broad vaccine uptake (ie, an estimated 55%–82% of the population) is needed to achieve effective population immunity [46], which undoubtedly will take some time. Vaccinating as many people as possible, including pregnant and breastfeeding people, will help attain such levels more quickly. Finally, many essential workers, particularly those who are currently pregnant, have anxiety about acquiring SARS-CoV-2 infection and transmitting the virus to family, patients, and coworkers [8]; vaccination would likely ameliorate these anxieties and provide welcomed relief and peace of mind for many.

IMPACT OF SARS-COV-2 VACCINATION ON FETUSES AND BREASTFEEDING INFANTS

While mRNA nanoparticle and adenovirus vector SARS-CoV-2 vaccines are not thought to pose significant risk to the recipient's fetus, important questions regarding fetal risk are only beginning to be answered [47, 48]. For instance, whether intact vaccine particles cross the placenta and enter fetal cells remains largely unknown, though studies of other lipid nanoparticle platforms suggest that they do not cross to the fetus [49]. The publication of preclinical DART study data and small human studies is helping to clarify such issues. For instance, 1

study evaluated 6 women after receipt of mRNA-based vaccines (5 received Pfizer/BioNTech and 1 received Moderna/NIH) and found no evidence of vaccine mRNA in breast milk samples collected within 2 days of vaccination [50].

Regarding whether maternal SARS-CoV-2 immunization leads to transfer of specific antibodies to infants, 1 study of 20 mother–infant pairs demonstrated efficient transplacental transfer of anti-SARS-CoV-2 spike antibodies after antenatal vaccination with the Pfizer/BioNTech vaccine [51], and another showed presence of vaccine-derived IgA antibodies in breastmilk 3–4 weeks postvaccination with the Pfizer/BioNTech (n = 14) and Moderna (n = 9) vaccines [52]. In the latter study, IgA antibody titers in breastmilk were similar to those of participants who had experienced natural SARS-CoV-2 infection. Such findings should encourage vaccination of breastfeeding people, among whom any theoretical risks related to vaccination are likely the same as those of the general population. Additionally, both Pfizer and Moderna are conducting clinical trials of their vaccines in children, and Janssen plans to start clinical trials in adolescents in March 2021, which will yield needed data on the safety, immunogenicity, and efficacy in these populations.

REGULATORY AND PROFESSIONAL BODY GUIDANCE ON SARS-COV-2 VACCINATION IN PREGNANCY

The paucity of data on SARS-CoV-2 vaccines in pregnant and breastfeeding populations makes counseling patients challenging. Many regulatory agencies in the United Kingdom and the United States have made recommendations regarding SARS-CoV-2 vaccination in pregnancy (Table 1). Advisory bodies in the United Kingdom, such as the MHRA and the Royal College of Obstetricians and Gynaecologists (RCOG), initially advised against offering SARS-CoV-2 vaccines to people who are pregnant and breastfeeding due to the lack of safety data in these populations [53], but they updated their positions on December 30, 2020 [54], recommending consideration of vaccination in those who are frontline personnel or those who have underlying conditions that put them at high risk of being infected with or experiencing serious complications of COVID-19, which includes pregnancy [54]. In contrast, the CDC's ACIP advises allowing all pregnant and breastfeeding people to choose whether to be vaccinated [21], and in the CDC's recommendations for prioritization of SARS-CoV-2 vaccine allocation, pregnancy is included as a "high-risk" condition eligible for vaccination during phase 1C [55]. Multiple reproductive medicine organizations, including the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), the American Society for Reproductive Medicine (ASRM), and the Academy of Breastfeeding Medicine (ABM), agree that SARS-CoV-2 vaccines should *not* be withheld from pregnant and breastfeeding people who are otherwise eligible [56].

Table 1. UK/US Advisory Body Recommendations on SARS-CoV-2 Vaccination of Pregnant and/or Lactating People

Advisory Body	Summary of Recommendations	Link to Recommendations
Public Health England/Medicines and Healthcare products Regulatory Agency (MHRA)	"As a matter of caution, COVID-19 vaccine is therefore not routinely advised in pregnancy but there are some circumstances in which the potential benefits of vaccination are particularly important for pregnant women."	https://www.gov.uk/government/publications/safety-of-covid-19-vaccines-when-given-in-pregnancy/the-safety-of-covid-19-vaccines-when-given-in-pregnancy
Royal College of Obstetricians and Gynaecologists (RCOG)	"Trials testing the vaccine in pregnant and breastfeeding women have not yet taken place. Whether to get the vaccine in pregnancy is your choice."	https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-24-combined-info-sheet-and-decision-aid.pdf
Centers for Disease Control and Prevention (CDC)	"Getting vaccinated is a personal choice. Any of the currently authorized COVID-19 vaccines can be offered to people who are pregnant or breastfeeding."	https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html
American College of Obstetricians and Gynecologists (ACOG)	"COVID-19 vaccines should not be withheld from pregnant individuals.... COVID-19 vaccines should be offered to lactating individuals similar to non-lactating individuals."	https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19
Society for Maternal-Fetal Medicine (SMFM)	"SMFM strongly recommends that pregnant and lactating people have access to the COVID-19 vaccines and that they engage in a discussion about potential benefits and unknown risks with their healthcare providers regarding receipt of the vaccine."	https://s3.amazonaws.com/cdn.smfm.org/media/2838/Provider_Considerations_for_Engaging_in_COVID_Vaccination_Considerations_3-3-21_(final).pdf
American Society for Reproductive Medicine (ASRM)	"Patients undergoing fertility treatment and pregnant patients should be encouraged to receive vaccination based on eligibility criteria. Since the vaccine is not a live virus, there is no reason to delay pregnancy attempts because of vaccination administration or to defer treatment until the second dose has been administered."	https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate13.pdf
Academy of Breastfeeding Medicine (ABM)	"The Academy of Breastfeeding Medicine does not recommend cessation of breastfeeding for individuals who are vaccinated against COVID-19. Individuals who are lactating should discuss the risks and benefits of vaccination with their health care provider, within the context of their risk of contracting COVID-19 and of developing severe disease."	https://www.bfmed.org/abm-statement-considerations-for-covid-19-vaccination-in-lactation

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Clearly, with all the above data (and lack thereof) and factors to consider, the decision of whether to undergo SARS-CoV-2 vaccination during pregnancy or while breastfeeding is a complex one. Health care provider counseling of pregnant people should focus on the available vaccine safety and efficacy data in the context of the individual's personal risk of SARS-CoV-2 exposure, underlying medical conditions, and SARS-CoV-2 prevalence in the community.

Several of the advisory bodies mentioned have published guides for counseling pregnant and lactating people as they contemplate the pros and cons of vaccination (eg, a "conversation guide" from ACOG can be found here: https://www.acog.org/-/media/project/acog/acogorg/files/pdfs/clinical-guidance/practice-advisory/covid19vaccine-conversationguide-121520-v2.pdf?la=en&hash=439FFEC1991B7DD3925352A5308C7C42; and SMFM provides "Provider Considerations for Engaging in COVID-19 Vaccine Counseling With Pregnant and Lactating Patients" here: https://s3.amazonaws.com/cdn.smfm.org/media/2838/Provider_Considerations_for_Engaging_in_COVID_Vaccination_Considerations_3-3-21_(final).pdf).

CONCLUSIONS

Because pregnant people were explicitly excluded from SARS-CoV-2 vaccine clinical trials, few data are available to guide them as they decide whether to undergo SARS-CoV-2 vaccination. Even so, given the reassuring safety and efficacy profiles of the SARS-CoV-2 vaccines that have gained UK/US regulatory authorization to date, the known risks of COVID-19 likely outweigh the unclear risks of SARS-CoV-2 vaccines for pregnant and breastfeeding people. Going forward, every effort should be made to collect data on the safety, immunogenicity, and efficacy of SARS-CoV-2 vaccines in pregnant and breastfeeding people through well-designed clinical trials that include these populations. As a matter of expediency, even when pregnant people are not included in initial vaccine clinical trials, once vaccine safety and immunogenicity are established in the general population, pregnant people should be included in vaccine studies as early as possible. In the meantime, it is important to remain transparent about the lack of information, acknowledge concerns, and support those who decide to defer vaccination until more data are available.

Acknowledgments

Financial support. No funding was used to support this article.

Potential conflict of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. None needed, as no individual patients are mentioned in this article.

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