Coronavirus disease 2019 vaccines in pregnancy

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As of December 1, 2020, nearly 64 million people have been infected with the severe acute respiratory syndrome coronavirus 2 worldwide with nearly 1.5 million global deaths. The impact of this virus has continued to overwhelm hospital infrastructure and demanded remodeling of healthcare systems. With rising concerns for a third, and possibly the largest, wave of individuals infected with the virus, national leaders are continuing to seek avenues by which we can further limit disease transmission and prevent infection with the use of vaccination. To our knowledge, no clinical trial evaluating vaccines to prevent coronavirus disease 2019 has included pregnant women. In December 2020, it was anticipated that the Food and Drug Administration will approve at least 1 or 2 mRNA-based coronavirus disease 2019 vaccine under the Emergency Use Authorization based on phase 3 clinical trial efficacy data. Both Pfizer and Moderna have manufactured mRNA-based vaccines with 95% and 94.1% efficacy against the severe acute respiratory syndrome coronavirus 2. AstraZeneca has manufactured a vaccine using a viral vector demonstrating early efficacy as well, and this next-generation platform has previously been utilized with the Ebola vaccine and safely administered during pregnancy with an acceptable safety profile. Approval of these vaccines will have a tremendous impact on the ongoing pandemic, yet there remains a lack of data for use of coronavirus disease 2019 vaccine in pregnant women. In this article, we seek to discuss the available data regarding treatment and prevention of coronavirus disease 2019 in pregnancy and address the growing questions regarding how best to approach vaccine access and administration in the pregnant population.

Key words: coronavirus disease 2019, maternal mortality, pandemic, pregnancy, remdesivir, vaccination, vaccine

Background

Coronavirus disease 2019 (COVID-19) is caused by a novel single-stranded RNA virus (severe acute respiratory syndrome coronavirus disease 2 [SARS-CoV-2]) that was first identified in Wuhan, China, in December 2019. The virus spreads through close contact from person to person primarily by respiratory droplets or nasal discharge, causing severe acute respiratory syndrome and, in some cases, multiorgan failure as a complication of an inflammatory cascade. Common symptoms include fever, headache, cough, fatigue, loss of sense of taste and smell, and respiratory symptoms. Although most individuals (>90%) infected with the virus are either asymptomatic or have mild symptoms, some people develop acute respiratory distress syndrome or other more severe forms of the disease, which can include thromboembolism, sepsis, or septic shock with multiorgan system failure. In some cases, symptoms may persist or worsen for months afterward; these individuals can recover from their initial illness and continue to have months of fatigue, cognitive impairment, muscle weakness, autonomic dysfunction, low-grade fevers, or persistent shortness of breath.[1–3]

Following a person's exposure, the incubation period, or time from exposure to symptom onset, for SARS-CoV-2 is typically 5 to 6 days. Once infected, individuals remain infectious for up to 10 days in moderate disease and 20 days in severe disease.[4] Individuals who are symptomatic and asymptomatic can spread the disease, and an individual who is symptomatic may be actively shedding the virus 1 to 3 days before symptom onset.[5–7]

As of December 1, 2020, there were approximately 13.6 million cases and 269,192 deaths associated with COVID-19 in the United States.[8] Racial and ethnic disparities have been seen during the COVID-19 pandemic with a higher incidence and disease prevalence among the Hispanic and Latino communities and a higher number of hospitalizations and deaths in the United States among black, non-Hispanic individuals. According to the Centers for Disease Control and Prevention (CDC), as of December 1, 2020, 1.27 million cases (24.4%) of COVID-19 have been in Hispanic and Latino individuals, with nearly 23,000 deaths (14.9%). Furthermore, 736,854 cases (14.2%) and 28,686 deaths (18.6%) from COVID-19 were in black, non-Hispanic individuals compared with 2.7 million cases (52.1%) and 88,067 deaths (57.1%) in white, non-Hispanic individuals. These demographic distributions can be compared with the most recent 2019 US census data in which 18% identified as Hispanic or Latino, 13.4% identified as black, and 59.7% identified as white. Disparities among these racial and ethnic groups have been well established[9,10] and likely result from an array of societal and structural racism factors

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leading to increased risk of exposure and more severe disease. Long-standing social inequities and discrimination may also contribute to the increased risk of severe disease and death from COVID-19.[11]

Initial reports based on limited data from China did not suggest an increase in maternal or infant mortality. In addition, 2 more recent publications evaluating pregnant and nonpregnant women in the United States with laboratory-confirmed SARS-CoV-2 have provided more information on disease incidence and related morbidity and mortality. In September 2020, Delahoy et al[12] found that among 598 hospitalized pregnant women with COVID-19 between March 2020 and August 2020, 326 (55%) were asymptomatic at admission. Pregnant women who were symptomatic were found to have more severe illness, including 44 (16.2%) requiring intensive care unit (ICU) admissions, 23 (8.5%) requiring mechanical ventilation, and 2 (1%) deaths. An additional study released in November 2020 looking at characteristics of women of reproductive age who were symptomatic with laboratory-confirmed SARS-CoV-2 infection by pregnancy status found that among approximately 400,000 women aged 15 to 44 years with symptoms of COVID-19, ICU admission (10.5 vs 3.9 per 1000 cases; adjusted relative risk [aRR], 3.0; 95% confidence interval [CI], 2.6−3.4), invasive ventilation (2.9 vs 1.1 per 1000 cases; aRR, 2.9; 95% CI, 2.2−3.8), extracorporeal membrane oxygenation (0.7 vs 0.3 per 1000 cases; aRR, 2.4; 95% CI, 1.5−4.0), and death (1.5 vs 1.2 per 1000 cases; aRR, 1.7; 95% CI, 1.2−2.4) were more likely in pregnant women than in nonpregnant women.[13] These data suggest that pregnant women should be counseled about the (1) likely increased risk of severe illness, including death; (2) proven measures to prevent SARS-CoV-2 infection; and (3) signs and symptoms for which to seek COVID-19 testing and treatment.

Prevention and Treatment

The ideal approach to address emerging infection in an epidemic and pandemic is prevention through social mechanisms and vaccination. The World Health Organization and CDC have recommended that all individuals wear face coverings in public settings to reduce the spread of the disease. In addition to face masks, implementation of social distancing guidelines has been recommended with the aim of reducing disease transmission. Proper handwashing and hygiene and the use of alcohol-based hand sanitizer in areas where soap and water are not readily available have been encouraged.

In addition to social distancing and personal hygiene guidelines, the biomedical industry has been busy trying to find effective drugs for the treatment and prevention of COVID-19. As of December 1, 2020, the New York Times Coronavirus Drug and Treatment Tracker had reported 22 different treatments for SARS-CoV-2 infection, with only one Food and Drug Administration (FDA)-approved drug available in the United States. Initially receiving Emergency Use Authorization (EUA), remdesivir was officially approved by the FDA in October 2020 for treating adults and adolescents diagnosed with mild to moderate COVID-19 requiring hospitalization. Remdesivir was shown in a double-blind, randomized, placebo-controlled trial to improve the median recovery time to 10 days for those who received remdesivir compared with 15 days among those who received placebo and reduce serious adverse events.[14]

Additional randomized treatment trials for COVID-19 are being performed worldwide, including a study in the United Kingdom, which showed that dexamethasone reduced mortality by one-third for critically ill patients on ventilators and by one-fifth for those receiving supplemental oxygen.[15] Following this publication, the National Institutes of Health (NIH) recommended the use of dexamethasone for patients requiring mechanical ventilation or supplemental oxygenation while hospitalized with COVID-19, including pregnant patients.[16]

To date, no randomized clinical treatment or vaccine trial of COVID-19 has focused on pregnant women, despite being deemed a high-risk population by the CDC.[17] Gilead Sciences, the maker of remdesivir, provided the drug for pregnant women who were hospitalized with severe COVID-19 under a compassionate use protocol.[18] Data from 86 pregnant women demonstrated recovery and serious adverse event rates comparable with those in the randomized trial, thus supporting the use of remdesivir in pregnant women under the subsequent FDA approval. Both remdesivir and dexamethasone are recommended for use in pregnant women by the NIH COVID treatment panel guidelines given the existing safety data and probable maternal benefit.[16] There are a number of other medications that have received EUA in recent weeks, including bamlanivimab, baricitinib combined with remdesivir, and the combinations of casirivimab and imdevimab. None of these are yet recommended for routine treatment of COVID-19 by the NIH.[16]

The US Department of Health and Human Services announced the framework for Operation Warp Speed on May 15, 2020, with the goal of delivering 300 million doses of a safe, effective vaccine to prevent COVID-19 by January 2021. As of December 1, 2020, the New York Times Coronavirus Vaccine Tracker had reported 57 different vaccines to prevent SARS-CoV-2 infection in human clinical trials with an additional 87 preclinical vaccines being studied in animals. Moderna was the first to launch the first-in-human phase 1 trial followed by a rapidly increasing number of clinical trials from numerous industry, federal, and foundation sponsors ranging phase 1 to 3 afterward.[19] Despite recommendations from public health advocates for pregnant women, including the CDC, American College of Obstetricians and Gynecologists (ACOG), and American Academy of Pediatrics, pregnant women have not been included in any phase 2 or phase 3 COVID-19 vaccine clinical trials to date.[20,21] Novel vaccines have been studied in pregnant women both during a pandemic situation, such as H1N1 influenza,[22] and outside a pandemic, such as recent trials of respiratory syncytial virus and group B streptococcus vaccines.[23,24] Although there are reported plans to enroll pregnant women

following the completion of phase 3 trials, no manufacturer has publicly released their timeline for the initiation of such studies.

Looking Ahead and Next Steps

There are currently 3 types of vaccines (mRNA vaccine, viral vector vaccine, protein subunit vaccine) being developed and investigated in clinical trials for COVID-19 in the United States. None of these types of vaccines can cause COVID-19 because these vaccines contain instructions for producing antigens that stimulate the body's immune system to produce antibodies against the SARS-CoV-2 proteins rather than containing the virus (or antigen) itself. mRNA vaccines work by supplying cellular material, promoting the production of SARS-CoV-2 proteins that stimulate the production of T and B lymphocytes. Vector vaccines work by exposing the body to a weakened version of a live virus inserted with SARS-CoV-2 genetic material, known as a viral vector. The viral vector promotes SARS-CoV-2 protein production, and the body creates copies of these proteins, stimulating the production of T and B lymphocytes. Protein subunit vaccines are injected pieces of proteins that cause SARS-CoV-2 infection. These proteins are recognized as foreign and stimulate the production of T lymphocytes. For each of these vaccine types, antibodies against SARS-CoV-2 proteins will then circulate following vaccination and be present to fight against future infection.[25]

By the end of December 2020, it is anticipated that the FDA will approve at least 1 mRNA-based COVID-19 vaccine under EUA based on phase 3 clinical trial efficacy data. Both Pfizer and Moderna have manufactured vaccines with greater than 90% efficacy against SARS-CoV-2 (Table). The primary efficacy analysis of Pfizer's BNT162b2 vaccine in more than 43,000 participants demonstrated 95% efficacy against SARS-CoV-2 infection beginning 28 days after the first dose, with 8 cases of COVID-19 in the vaccine group vs 162 cases in the placebo group. In addition, 10 cases of severe COVID-19 occurred in the placebo group and 1 case in the BNT162b2-vaccinated group. The vaccine was well tolerated across all populations with no serious safety concerns. Minor side effects included fatigue and headache following the second vaccine dose.[29] On November 20, 2020, Pfizer and BioNTech submitted a request to the FDA for EUA of their COVID-19 vaccine candidate. Moderna's mRNA-1273 vaccine of 30,000+ participants reported 94.1% efficacy, with 11 cases of COVID-19 in the vaccine group vs 185 cases in the placebo group. Furthermore, 30 cases of severe COVID-19 were identified in the placebo group compared with 0 cases in the mRNA-1273—vaccinated group. Minor side effects reported being fatigue, muscle pain, headache, and pain at injection site.[30] Moderna filed their request for EUA with the FDA on November 30, 2020. Approval of these vaccines and potentially others in the future will have an incredible impact on ending the current pandemic for much of the population worldwide. However, the lack of data on any COVID-19 vaccines in pregnant women raises many questions and concerns on how best to approach vaccine access and administration during pregnancy.

In additional to vaccine distribution and accessibility, cost remains a question. Pfizer and BioNTech have set an initial price at $19.50 per dose or $39 per patient for a full 2-dose regimen. Moderna has set an initial price at $25 per dose or $50 per patient for a full 2-dose regimen. Those prices remain similar to seasonal influenza vaccine, which can cost near $40 for uninsured patients and included under preventive services for individuals with insurance. Most commercial insurers and self-funded employer health plans will be expected to cover costs for COVID-19 vaccines though regulations established by the Departments of Labor and Treasury. Similarly, the Centers for Medicare and Medicaid Services have finalized that any FDA-approved COVID-19 vaccine will be provided with no cost coverage for seniors and individuals enrolled in government-funded health insurance programs.[27]

Recommendations

Assuming COVID-19 vaccines are approved for EUA, numerous questions will follow regarding recommendations for use in pregnant and lactating individuals. The ACOG, Society for Maternal-Fetal Medicine (SMFM), NIH, and National Academy of Medicine have consistently advocated the inclusion of pregnant and lactating women in vaccine trials.[28,31,32] In addition, on December 1, 2020, the SMFM released a statement strongly recommending that pregnant women have access to COVID-19 vaccines in all phases of future vaccine campaigns. This recommendation includes healthcare workers, who are being considered a priority for vaccination, be offered the vaccine if pregnant. The authors note that COVID-19 is an active outbreak, that pregnancy is associated with increased susceptibility to disease severity, and that the best approach to protect the infant is through passive placental antibody transfer.[33]

Considering the data available regarding increased maternal morbidity and mortality associated with SARS-CoV-2 infection in pregnancy,[12,13] withholding FDA-approved vaccines from this population based on theoretical risks would be unethical. Vaccination of women against seasonal influenza, pertussis, and tetanus during pregnancy is based on the increased risks that these infections pose to the mother and/or infant and the well-established safety profiles for these inactivated and protein-antigen—based licensed vaccines. Other vaccinations are approved worldwide for special circumstances when the risk of exposure to a serious illness is high, as in the case of meningococcal A and yellow fever.[34] The safety assessment of immunization in pregnancy involves evaluation of adverse events. Vaccines are immunogenic, and patients may experience body aches, fevers, and headaches for a few days following vaccination. These acceptable, and non—life-threatening, side effects of vaccination would need to be recognized

TABLE
Pfizer-, Moderna-, and AstraZeneca-manufactured vaccines

COVID-19 vaccine	Type of vaccine	n/N	Results	Efficacy (%)	Safety profile	Side effects
Pfizer Inc and BioNTech SE (*BNT162b2*)	mRNA	170/ 43,661	Vaccine group: • 8 cases COVID-19 • 1 case severe COVID-19	95[a]	Well tolerated and efficacy consistent across age, gender, race, and ethnicity	Fatigue (3.8%)
			Placebo group: • 162 cases COVID-19 • 10 cases severe COVID-19		No serious safety concerns to date	Headache (2.0%)
						Requires temperature control and continued storage at (−70°C or −94°F)
Moderna (*mRNA-1273*)	mRNA	196/ 30,000+	Vaccine group: • 11 cases COVID-19 • 0 cases severe COVID-19	94.1	Well tolerated and efficacy consistent across age, gender, race, and ethnicity	Fatigue
			Placebo group: • 185 cases COVID-19 • 30 cases severe COVID-19 • 1 death from COVID-19		No serious safety concerns to date	Headache
						Myalgias
						Pain or erythema at injection site
						Requires temperature control (−20°C or −4°F); can be stored in refrigerated conditions for 1 mo
AstraZeneca (*AZD1222*)	Viral vector	131/ 11,363	Dosing regimen efficacy: • Half dose followed by full dose >30 d: 90% • Full dose followed by full dose >30 d: 62%	70[b]	Well tolerated across both dosing regimens	Not reported to date
			0 cases of severe COVID-19		No serious safety concerns to date	Can be stored, transported, and handled at normal refrigerated conditions (2°C–8°C) for at least 6 mo

n indicates confirmed cases of COVID-19; N indicates total number of participants enrolled.

COVID-19, coronavirus disease 2019; *FDA*, Food and Drug Administration.

Adapted from Pfizer and BioNTech, Moderna, and AstraZeneca.[29,30,26]

[a] Beginning 28 days after receiving the first dose; [b] Beginning 14 days after receiving 2 doses.

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and considered when evaluating mothers, understanding that these side effects may prompt additional evaluations for pregnancy-related morbidities, including sepsis and preeclampsia, that can present with similar complaints.

The fetal impact of COVID-19 vaccination is unknown, and the potential for fetal risk must be acknowledged. There is a theoretical risk of fetal harm from any untested medical intervention, and this is no different for COVID-19 vaccines.

Box
Major considerations related to pregnancy and COVID-19 vaccination

Major considerations related to pregnancy and COVID-19 vaccination

- COVID-19 infection in pregnancy is associated with increased risk of morbidity and mortality
- Large proportion of healthcare workers are pregnant and will be potentially eligible to receive vaccine before studies can be done in pregnancy
- FDA-approved vaccines should not be withheld from women solely based on their pregnancy or lactation status when they otherwise meet criteria for vaccination
- Withholding vaccine violates ethical principle of autonomy, as well as beneficence and justice

COVID-19, coronavirus disease 2019; *FDA*, Food and Drug Administration.
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Pregnant individuals should be given the opportunity, along with their obstetrical provider, to weigh the potential risk of severe maternal disease against the unknown risk of fetal exposure and make an autonomous decision about whether or not to accept the vaccine until pregnancy safety data are available (Box).

As the COVID-19 pandemic continues and the FDA authorizes COVID-19 vaccines for use in the US population, it is possible that these vaccines will be allowed to be administered to pregnant women despite the lack of data. Preparation and planning for safety assessment through existing mechanisms, such as the CDC's Vaccine Adverse Event Reporting System, Vaccine Safety Datalink, and Clinical Immunization Safety Assessment (CISA) Project would be prudent.[35] Through the CISA Project, the CDC recently funded the Duke University to coordinate and conduct a multisite prospective observational study to evaluate the safety of COVID-19 vaccines in pregnant women who are immunized under standard of care practices (CDC 200-2012-53663). In addition, the CDC is launching a smartphone-based application called V-SAFE, which will utilize text messaging and surveys to monitor vaccinated individuals daily for the first week and then weekly for 6 weeks. V-SAFE will collect data on pregnancy status, including gestational age or postpartum state, at the time of vaccination. The application will monitor for fevers, chills, and other symptoms and medically significant adverse events with active follow-up, including a telephone call from a provider as indicated.[36]

Summary

Based on increased COVID-19–related morbidity and mortality during pregnancy combined with the currently available efficacy and safety profile of COVID-19 vaccines in nonpregnant people, FDA-approved COVID-19 vaccines should not be withheld from women solely based on their pregnancy or lactation status when they otherwise meet the criteria for vaccination. Patient-provider discussions should consider the patient's individual risk-benefit profile regarding exposure at work or at home, exposing members of their household, current health status, and perceived risk of COVID-19–related complications. ■

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