COVID-19 Vaccines in Pregnancy

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Condensation: COVID-19 vaccines should not be withheld from women solely based on their pregnancy or lactation status, when they otherwise meet criteria for vaccination.

Short Title: COVID-19 vaccines in pregnancy

AJOG at a Glance:

- Why was the study conducted?
  - With emerging data surrounding COVID-19 vaccines, questions remain regarding the safety and efficacy profiles of these vaccines in pregnant women.
- What are the key findings?
  - We explain the evidence currently available regarding treatment of COVID-19 in pregnancy and data to support the use and accessibility of COVID-19 vaccines in pregnant women. Upcoming trials should include this high risk population to investigate vaccine safety and efficacy in pregnancy.
- What does this study add to what is already known?
  - FDA-approved COVID-19 vaccines should not be withheld from women solely based on their pregnancy or lactation status, when they otherwise meet criteria for vaccination. Considering data available regarding increased maternal morbidity and mortality associated with COVID-19 infection in pregnancy, withholding FDA approved vaccines from this population based on theoretical risks would be unethical.

Keywords: COVID-19, vaccine, vaccination, pregnancy, remdesivir, maternal mortality, pandemic

Unstructured Abstract

As of December 1, 2020, nearly 64 million people have been infected with COVID-19 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 infected individuals, 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 COVID-19 has included pregnant women. By December 2020, it's anticipated that the FDA will approve at least one or two mRNA-based COVID-19 vaccine under emergency use authorization (EUA) based on Phase 3 clinical trial efficacy data. Both Pfizer and Moderna have manufactured mRNA-based vaccines with 95% and 94.1% efficacy against COVID-19. [1, 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 [3]. Approval of these vaccines will have a tremendous impact on the ongoing pandemic, yet there remains a lack of data for use of COVID-19 vaccine in pregnant women. In this article we seek to discuss the available data regarding treatment and prevention of COVID-19 in pregnancy and address the growing questions regarding how best to approach vaccine access and administration in the pregnant population.

Main Text

Background

Coronavirus disease 2019 (COVID-19) is caused by a novel single stranded RNA virus (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 the majority (>90%) of infected individuals are either asymptomatic or have mild symptoms, some people develop acute respiratory distress syndrome (ARDS) 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 afterwards; 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. [4-6]

Following a person's exposure, the incubation period, or time from exposure to symptom onset, for COVID-19 is typically 5-6 days. Once infected, individuals remain infectious for up to ten days in moderate disease and twenty days in severe disease. [7] Both symptomatic and asymptomatic individuals can spread the disease and a symptomatic individual may be actively shedding virus one to three days prior to symptom onset. [8-10]

As of December 1, 2020, there were ~ 13.6 million cases and 269,192 deaths associated with COVID-19 in the United States. [11] Racial and ethnic disparities have been seen during the

COVID 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 CDC, as of December 1, 2020, 1.27 million (24.4%) cases of COVID-19 have been in Hispanic/Latino individuals, with nearly 23,000 (14.9%) deaths. 736,854 (14.2%) cases and 28,686 (18.6%) deaths from COVID-19 were in Black, Non-Hispanic individuals compared to 2.7 million (52.1%) cases and 88,067 (57.1%) deaths in White, Non-Hispanic individuals. These demographic distributions can be compared to the most recent 2019 United States census data in which 18% identified as Hispanic/Latino, 13.4% identified as Black, and 59.7% identified as White. Disparities among these racial and ethnic groups have been well established [12, 13] and likely result from an array of societal and structural racism factors leading to increased risk for exposure and more severe disease. Long-standing social inequities and discrimination may also contribute to increased risk for severe disease and death from COVID-19. [14]

Initial reports based on limited data from China did not suggest an increase in maternal or infant mortality. Two more recent publications evaluating pregnant and non-pregnant women in the United States with laboratory-confirmed SARS-CoV-2 have provided more information on disease incidence as well as related morbidity and mortality. In September 2020, Delahoy et al found that among 598 hospitalized pregnant women with COVID-19 between March and August of 2020, 55% (n=326) were asymptomatic at admission. Symptomatic pregnant women were found to have more severe illness including 44 (16.2%) requiring intensive care unit admissions, 23 (8.5%) requiring mechanical ventilation, and two (1%) deaths. [15] An additional

study released in November 2020 looking at characteristics of symptomatic women of reproductive age with laboratory confirmed SARS-CoV2 infection by pregnancy status found that among approximately 400,000 women aged 15 – 44 years old with symptomatic COVID-19, intensive care unit admission (10.5 versus 3.9 per 1,000 cases; aRR=3.0, 95% CI=2.6-3.4), invasive ventilation (2.9 versus 1.1 per 1,000 cases; aRR=2.9; 95% CI 2.2-3.8), extracorporeal membrane oxygenation (ECMO) (0.7 versus 0.3 per 1,000 cases; aRR=2.4; 95% CI 1.5-4.0), and death (1.5 versus 1.2 per 1,000 cases; aRR=1.7; 95% CI 1.2-2.4) were more likely in pregnant than in nonpregnant women. [16] These data suggest that pregnant women should be counseled about the 1) likely increased risk for severe illness, including death, 2) proven measures to prevent COVID-19 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 (WHO) and the Centers for Disease Control and Prevention (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 at reducing disease transmission. Proper hand-washing and hygiene has been encouraged, as well as the use of alcohol-based hand sanitizer in areas where soap and water are not readily available.

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 COVID-19 infection, with only one Food and Drug Administration (FDA)-approved drug available in the US. Initially receiving emergency-use authorization (EUA), remdesivir was officially approved by the FDA in October 2020 for treatment of adults and adolescents with mild to moderate COVID-19 diagnosis 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 to 15 days among those who received placebo and reduce serious adverse events. [17]

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. [18] Following this publication, the National Institutes of Health (NIH) went on to recommend the use of dexamethasone for patients requiring mechanical ventilation or supplemental oxygenation while hospitalized with COVID-19, including pregnant patients. [19]

To date, no randomized clinical treatment or vaccine trials for COVID-19 has focused on pregnant women, despite being deemed a high risk population by the CDC. [20] Gilead Sciences, the maker of remdesivir, provided the drug for hospitalized pregnant women with severe COVID-19 infection under a compassionate use protocol. [21] Data from 86 pregnant

women demonstrated recovery and serious adverse event rates comparable to 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. [19] There are a number of other medications that have received EUA in recent weeks, including bamlaminivimab, 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. [19]

The United States Department of Health and Human Services announced the framework for Operation Warp Speed (OWS) on May 15, 2020, with the goal of delivering 300 million doses of a safe, efficacious 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 COVID-19 infection in human clinical trials with an additional 87 preclinical vaccines being studied in animals. Moderna, Inc. 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 – 3 thereafter. [22] Despite recommendations from public health advocates for pregnant women, including the CDC, the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP), pregnant women have not been included in any Phase 2 or Phase 3 COVID-19 vaccine clinical trials to date. [23, 24] Novel vaccines have been studied in pregnant women both during a pandemic situation like H1N1 influenza [25] and outside a pandemic such as recent trials of RSV

and GBS vaccines. [26, 27] Although there are reported plans to enroll pregnant women following completion of Phase 3 trials, no manufacturer has publicly released their timeline for initiation of such studies.

Looking Ahead & Next Steps

There are currently three 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 (Table). None of these types of vaccines can cause COVID-19 because rather than containing the virus (or antigen) itself, these vaccines contain instructions for producing antigens which stimulate the body's immune system to produce antibodies against the COVID-19 proteins. mRNA vaccines work by supplying cellular material which promote production of COVID-19 proteins that stimulate production of T-lymphocytes and B-lymphocytes. Vector vaccines work by exposing the body to a weakened version of a live virus inserted with COVID-19 genetic material, known as a viral vector. The viral vector promotes COVID-19 protein production and the body makes copies of these proteins which stimulates production of T-lymphocytes and B-lymphocytes. Protein subunit vaccines are injected pieces of proteins that cause COVID-19. These proteins are recognized as foreign and stimulate production of T-lymphocytes. For each of these vaccine types, antibodies against COVID-19 proteins will then circulate following vaccination and be present to fight against future infection. [28]

By the end of December 2020, it is anticipated that the FDA will approve at least one mRNA-based COVID-19 vaccine under emergency use authorization (EUA) based on Phase 3 clinical trial efficacy data. Both Pfizer and Moderna have manufactured vaccines with greater than 90%

efficacy against COVID-19. (Table) Primary efficacy analysis of Pfizer's BNT162b2 vaccine in over 43,000 participants demonstrated 95% efficacy against COVID-19 beginning 28 days after the first dose, with 8 cases of COVID-19 in the vaccine group versus 162 cases in the placebo group. 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. [1] On November 20, 2020, Pfizer/BioNTech were the first to submit 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 versus 185 cases in the placebo group. Thirty cases of severe COVID-19 were identified in the placebo group, compared to zero cases in the mRNA-1273 vaccinated group. Minor side effects reported being fatigue, muscle pain, headache, and pain at injection site. [2] 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 any 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 initial price at $19.50 per dose, or $39 per patient for full two-dose regimen. Moderna has set initial price at $25 per dose, or $50 per patient for full two-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. [29]

Recommendations

Assuming COVID-19 vaccines are approved for EUA, numerous questions will follow regarding recommendations for use in pregnant and lactating individuals. The American College of Obstetrics & Gynecology (ACOG), Society for Maternal-Fetal Medicine (SMFM), National Institutes of Health (NIH) and National Academy of Medicine have consistently advocated for the inclusion of pregnant and lactating women in vaccine trials. [30-32] Additionally, on December 1, 2020, 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 prioritized for vaccination, be offered the vaccine if pregnant. Authors note that COVID-19 is an active outbreak, that pregnancy is associated with increased susceptibility disease severity, and that the best approach to protect the infant is through passive placental antibody transfer. [33]

Considering data available regarding increased maternal morbidity and mortality associated with COVID-19 infection in pregnancy [15,16], withholding FDA approved vaccines from this

population based on theoretical risks would be unethical (Box). 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 as well as 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 (AEs). Vaccines are immunogenic and patients may experience body aches, fevers, and headaches for a few days following vaccination. These acceptable, and not life-threatening, side effects of vaccination would need to be recognized 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 for fetal harm from any untested medical intervention and this is no different for COVID-19 vaccines. Pregnant individuals should be given the opportunity, along with their obstetric 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 vaccine until pregnancy safety data are available.

As the COVID-19 pandemic continues and the FDA authorizes COVID-19 vaccine(s) for use in the U.S. 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 (VAERS), Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) Project would be prudent. [35] Through the CISA Project, CDC recently funded Duke University to coordinate and conduct a multi-site 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 six weeks. V-SAFE will collect data on pregnancy status, including gestational age or postpartum state, at time of vaccination. The application will monitor for fevers, chills, and other symptoms as well as 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 non-pregnant people, FDA-approved COVID-19 vaccines should not be withheld from women solely based on their pregnancy or lactation status, when they otherwise meet criteria for vaccination (Box). 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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Table
Selected COVID-19 vaccines

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

*beginning 28 days after receiving the first dose
**beginning 14 days after receiving two doses
(n)= confirmed cases of COVID-19; N= total number of participants enrolled
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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