The coronavirus disease 2019 vaccine in pregnancy: risks, benefits, and recommendations

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The coronavirus disease 2019 has caused over 2 million deaths worldwide, with over 412,000 deaths reported in Unites States. To date, at least 57,786 pregnant women in the United States have been infected, and 71 pregnant women have died. Although pregnant women are at higher risk of severe coronavirus disease 2019—related illness, clinical trials for the available vaccines excluded pregnant and lactating women. The safety and efficacy of the vaccines for pregnant women, the fetus, and the newborn remain unknown. A review of maternal and neonatal coronavirus disease 2019 morbidity and mortality data along with perinatal vaccine safety considerations are presented to assist providers with shared decision-making regarding vaccine administration for this group, including the healthcare worker who is pregnant, lactating, or considering pregnancy. The coronavirus disease 2019 vaccine should be offered to pregnant women after discussing the lack of safety data, with preferential administration for those at highest risk of severe infection, until safety and efficacy of these novel vaccines are validated.

Key words: coronavirus, lactation, coronavirus disease 2019, COVID-19 vaccine, influenza A H1N1, maternal immunity, Middle East respiratory syndrome, mRNA vaccine, severe acute respiratory syndrome coronavirus 2, severe acute respiratory syndrome, vaccine safety, Zika

The Coronavirus Disease 2019 Vaccine During Pregnancy: Risks, Benefits, and Recommendations

The current coronavirus disease 2019 vaccines

As of January 23, 2021, over 98 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported worldwide. In the United States, over 24 million people have been infected and at least 400,000 people have died because of SARS-CoV-2 infection.[1–4] The pressing need for therapeutics and vaccines to treat and prevent coronavirus disease 2019 (COVID-19)-related illness and its effect on our global economic structure resulted in multiple research studies seeking effective tools to combat this disease.[5–12] With the support of the US Department of Health and Human Services (DHHS), multiple researchers and pharmaceutical companies are actively pursuing the development and manufacture of efficacious and timely vaccines against this virus.[5–12] On December 11, 2020, the Federal Drug Administration (FDA) issued the first Emergency Use Authorization (EUA) for Pfizer-BioNTech's mRNA COVID-19 vaccine.[13,14] This allowed the vaccine to be nationally distributed to adults aged ≥16 years using the safety and efficacy data from their global trial.[13–16] Vaccine efficacy was demonstrated to be 95% in preventing symptomatic and laboratory-confirmed COVID-19 among persons without evidence of previous infection for 7 days after the second dose was administered.[13–16] Shortly after, on December 18, 2020, Moderna, Inc, was issued an EUA after the safety and immunogenicity of their mRNA SARS-CoV-2 vaccine data were published and efficacy was demonstrated to be 94.1% against symptomatic and laboratory-confirmed infection in participants aged ≥18 years without evidence of previous infection for 14 days after completion of the 2-dose series.[17–21] Although not yet approved in the United States, the Oxford-AstraZeneca vaccine was approved by the British Department of Health and Social Care in the United Kingdom on December 30, 2020 after the vaccine was shown to have a pooled efficacy of 70.4% in preventing symptomatic and laboratory-confirmed COVID-19 14 days after completion of the 2-dose series among adults without previous infection.[22,23] Detailed summary data for the approved SARS-CoV-2 vaccines are presented in Table 1. On December 13, 2020, and December, 20, 2020, the Advisory Committee on Immunization Practices (ACIP) branch of the Centers for Disease Control and Prevention (CDC) issued an interim recommendation for use of the Pfizer-BioNTech and Moderna COVID-19 vaccines, respectively, after the designated COVID-19 working group reviewed the evidence for vaccine efficacy and safety and implementation considerations, including offering them to eligible pregnant and lactating women, despite their exclusion from these clinical trials.[13–24]

Coronavirus disease 2019 in pregnancy

Mechanical and physiological alterations in pregnancy increase susceptibility to certain infections.[25–27] The immunologic alterations that occur during pregnancy not only may be protective to the fetal allograft but also may create vulnerability to certain viral infections.[25–27] More than 1600 reports

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Received Jan. 12, 2021; revised Jan. 24, 2021; accepted Jan. 25, 2021.

The authors report no conflict of interest.

This work has not been published previously and is not under consideration for publication elsewhere.

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0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2021.01.022

TABLE 1
Summary of available SAR-CoV-2 vaccines

Name	Vaccine type	Experimental design	Primary outcome	Secondary	Results
Pfizer-BioNTech	mRNA BNT162b2	Double-blinded RCT 1:1 ratio of vaccine to placebo	Efficacy against COVID-19 >7 d after second dose defined by:	1) Severe COVID-19[d]	1) Without previous COVID-19: 95.0% efficacy (95% CI, 90.3–97.6)
		2 doses, 21 d apart	a) Symptomatic[a]	2) Safety or side effects	2) With or without previous COVID-19: 94.6% efficacy (95% CI, 89.9–97.3)
		≥16 y old	b) NAAT	3) Efficacy after first dose	3) Systemic complaints: first dose, 52%–59%; second dose, 39%–51%
		N=43,448	within 4 days of symptom onset[b]	4) In persons with or without COVID-19	
		Multicenter, international	In persons without previous COVID-19[c]		
		Probability of vaccine efficacy >30%			
		95.0% credible interval for vaccine efficacy			
		Bayesian beta-binomial mode			
Moderna	mRNA-1273	Observer-blinded RCT 1:1 ratio of vaccine to placebo	Efficacy against COVID-19 >14 d after second dose defined by:	1) Severe COVID-19[d]	1) Without previous COVID-19: 94.1% efficacy (95% CI, 89.3–96.8)
		2 doses, 28 d apart	a) Symptomatic[e]	2) Safety or side effects	2) In persons with previous COVID-19: 93.6% (95% CI, 88.6–96.5)
		≥18 y old	b) NAAT	3) Efficacy after first dose	3) Systemic complaints: first dose, 54.9%; second dose, 79.4%
		N=30,420	within 4 days of symptom onset[f]	4) In persons with and without previous COVID-19	
		Multicenter, United States	In persons without previous COVID-19[c]		
		Probability of vaccine efficacy >30%			
		1-sided O'Brien-Fleming boundary for efficacy. Lan-DeMets alpha-spending for efficacy boundaries			

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(continued)

TABLE 1
Summary of available SAR-CoV-2 vaccines *(continued)*

Name	Vaccine type	Experimental design	Primary outcome	Secondary	Results
Oxford-AstraZeneca	Adenovirus-vectored vaccine	Single-blind and double-blind (1 site) RCT 1:1 ratio of vaccine to placebo 28 d apart	Efficacy against COVID-19 >14 d after second dose defined by:	1) Efficacy after both doses, full dose	1) Persons without previous COVID-19: vaccine efficacy: 90.0% (67.4 −97.0) for 0.5 and full dose
		Subset: 0.5 and full dose second dose	a) Symptomatic[g]	2) Safety or side effects	2) Vaccine efficacy: 62.1% (95% CI, 41.0−75.7) 2 full doses
		≥18 y old	b) NAAT[h]	3) Efficacy in patients with previous COVID-19	3) 1.6% severe side effects
		N=23,848	In persons without previous COVID-19[c]		
		Multicenter, international	Primary: efficacy after first dose is 0.5 dose		
		Vaccine efficacy Poisson regression model adjusted for age	Excluded if NAAT is positive within 14 d after second dose		

CI, confidence interval; *COVID-19*, coronavirus disease 2019; *FDA*, Food and Drug Administration; *NAAT*, Nucleic acid amplification-based test; *NP*, nasopharyngeal; *RCT*, randomized controlled trial; *RT-PCR*, reverse transcription-polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

[a] Pfizer: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting; [b] Respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification-based testing; [c] Participants were assessed for the presence of SARS-CoV-2—binding antibodies specific to the SARS-CoV-2 nucleocapsid protein and had a nasopharyngeal swab for SARS-CoV-2 RT-PCR testing using protocol-defined acceptable tests; [d] Severe COVID-19 as defined by the FDA includes severe systemic illness, respiratory failure, evidence of shock, significant acute renal, hepatic, or neurologic dysfunction; admission to the intensive care unit; or death; [e] Moderna: 2 or more the following symptoms: fever (temperature of ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder or occurring in those who had at least 1 respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia); [f] One NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR; [g] AstraZeneca: temperature of >37.8°C, cough, shortness of breath, and anosmia or ageusia. In some sites, the list of qualifying symptoms for swabbing was broader and included myalgia, chills, sore throat, headache, nasal congestion, diarrhea, runny nose, fatigue, nausea, vomiting, and loss of appetite; [h] One NP swab or nasal swab positive for SARS-CoV-2 by RT-PCR by home kits using protocol-defined acceptable tests.

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evaluating COVID-19 and pregnancy have been published. Most reports are cohort studies, case series, and meta-analyses describing diagnostic challenges, therapeutic options, intrauterine transmission, and perinatal complications among affected pregnancies. Although several studies, including a recent meta-analysis with data from over 435 pregnant women with infection have suggested that the severity of COVID-19 in pregnant women is similar to nonpregnant adults,[28−34] CDC data and other publications indicate an increased risk of intensive care unit (ICU) admission (10.5 vs 3.9 per 1000 cases; adjusted risk ratio [aRR], 3.0; 95% confidence interval [CI], 2.6−3.4), mechanical ventilation (2.9 vs 1.1 per 1000 cases; aRR, 2.9; 95% CI, 2.2−3.8), and death (1.5 vs 1.2 per 1000 cases; aRR, 1.7; 95% CI, 1.2−2.4) in pregnant patients with symptomatic COVID-19 infection compared with nonpregnant women after adjusting for age, race, ethnicity, and comorbidities, with even higher risk for subgroups of women who are underserved, have comorbidities, or are of advanced maternal age.[35−45] However, these surveillance data have limitations, as over 64.5% of total cases involving women did not have pregnancy status recorded.[45] In addition, among those with known pregnancy status, race and ethnicity status was missing for 25% of cases, and information on symptoms and underlying conditions was missing for approximately half of the participants.[45] A recent publication of morbidity, mortality, and pregnancy outcome of over 400,000 women admitted for delivery with and without COVID-19 collected from an all-payer database of 20% of US hospitals demonstrated similar outcomes, reporting an increased rate of death in women with infection compared to those without COVID-19 (number of deaths per 100,000 women, 141 [95% CI, 65−268] vs 5.0 [95% CI, 3.1−7.7]).[46] Despite limited evidence that the infection increases other adverse pregnancy outcomes, there remains a higher risk of thromboembolic disease, hypertensive disorders, preterm birth, and cesarean delivery for pregnant

women with infection, differentially represented across global regions.[28–46] Although the absolute risk for severe infection is low, the CDC has included pregnancy as a risk factor for severe COVID-19, and this has been echoed by the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), and other women's health organizations.[47–53]

Several reports of neonatal transmission and adverse outcomes for newborns with infection have been reported; however, some of these data are confounded by uncertainty surrounding testing and diagnostics for these neonates and other independent neonatal morbidities.[54–60] Collectively, the current available data suggest an approximate 2% to 3% risk of vertical transmission with a minimal rate of persistent neonatal infection. Consistent with these observations are data showing that SARS-CoV-2 is not routinely detected in amniotic fluid, cord blood, or neonatal nasopharyngeal samples associated with affected pregnancies.[54–60] Several studies have described the detection of viral RNA in breast milk of mothers with infection; however, there is no evidence to suggest that the ingestion of breast milk from mothers with SAR-CoV-2 infection increases the risk of transmission to their newborns.[61–63] Variable quantities of immunoglobulin A antibodies were detected in 80% of 18 breast milk samples collected from women with infection in 1 study; however, the protective capacity of these antibodies against infection for newborns and infants requires further investigation.[61–63]

Past pandemics and vaccine safety in pregnant women

Disproportionate rates of maternal morbidity, adverse perinatal outcomes, and mortality because of infectious disease have been described in past pandemics. During the 2002 severe acute respiratory syndrome (SARS) pandemic, which infected over 8000 people in 26 countries, maternal case fatality was 25%, and miscarriage occurred in 57% of pregnant women with infection.[64–70] The Middle East respiratory syndrome, another coronavirus, has demonstrated similar pathogenicity, leading to adverse perinatal events in over 90% of women with infection in 2012.[64–70] Currently, a safe and efficacious vaccine has not been developed for these pathogens. In 2009, a novel strain of the influenza A virus, termed H1N1, resulted in a pandemic with an estimated 40 million people infected between April 2009 and April 2010, resulting in more than 274,304 hospitalizations and 12,469 deaths.[64–74] During the first 5 months of the H1N1 pandemic, 788 cases were reported in pregnant women. Of those cases, 30 pregnant women died, comprising 5% of all reported 2009 influenza H1N1 deaths during this period.[67–74] Furthermore, 4 case reports of suspected H1N1 vertical transmission in newborns have been published, with 1 reported neonatal death.[75–77,78] In addition, observational studies have demonstrated higher frequencies of maternal infectious morbidity, showing higher rates of maternal ICU admission and death because of H1N1 influenza infection compared with rates in nonpregnant populations, even more so than the rates of the current COVID-19 pandemic.[79,80]

Vaccines and reproductive toxicology

Although several vaccine efficacy and safety studies were conducted with pregnant and lactating women during the H1N1 pandemic, the COVID-19 vaccine trials have excluded these groups, and therefore, critical perinatal safety information remains largely unknown.[13–24,81] The mRNA (Pfizer-BioNTech and Moderna) and viral vector (AstraZeneca) COVID-19 vaccines are novel in design and, to date, are the first mRNA and viral vector vaccine trials to have been comprehensively evaluated for disease prevention in people.[13–23,81] Of note, the Ebola vaccine (rVSVΔG-ZEBOV-G, Merck) was developed using similar viral vector technology and is currently approved for disease prevention in nonpregnant adults.[81] Several preliminary human studies have demonstrated promising safety and immunogenicity data using the mRNA vaccine model with other pathogens, including the influenza virus, Zika virus, and rabies virus,[81–88] but previous efficacy studies evaluating mRNA vaccines during pregnancy are limited to animal studies involving the Zika virus, where vaccination resulted in a significant reduction of placental and fetal viral burden.[81–88] Details concerning transplacental vaccine transfer have not been described.[81–88] Although disclosed details of the protocols are available for review, the precise formulations of the cationic nanoparticles used for mRNA assembly of the COVID-19 vaccines remain propriety to the manufacturing pharmaceutical companies and preliminary safety data regarding the COVID-19 mRNA vaccines during gestation reference a perinatal or postnatal reproductive toxicology study in rats, which demonstrated no safety alert.[13–23,47]

Ultimately, the advantage of past and present influenza vaccine designs in comparison is the background benefit of known published protocols and historic experience utilizing inactivated or attenuated virus since 1940, leading to a more expeditious design for safety and efficacy.[89–95] These studies were accomplished with fewer challenges compared with the de novo human vaccine development for the novel SARS-CoV-2.[13–23,81] Typically, vaccines intended for pregnant or breastfeeding women rely on critical review by the scientific community of all observational studies, case reports and series, registries and experimental data regarding the type of vaccine, pathogen placental transfer studies, toxicity and immunogenicity studies, and trimester-specific infection risks. These reviews are conducted through collaborative efforts by the Vaccine Safety Datalink, a collaborative project between the CDC and others, including the ACIP Workgroup, National Institutes of Health, Task Force on Research Specific to Pregnant Women and Lactating Women, World Health Organization, and Global Advisory Committee on Vaccine Safety.[89–100]

Priority is granted to potential vaccines that meet several key criteria when considered for mass vaccination campaigns.[96–108] The vaccine should demonstrate the potential to reduce morbidity in the pregnant woman and/or her fetus. In addition, there should exist a lack of evidence of adverse pregnancy outcomes or potential harm to the fetus or mother with vaccine exposure.[96–108]

Multiple randomized control trials and prospective studies have demonstrated vaccine efficacy against influenza-related morbidity in the pregnant patient and laboratory-confirmed infection in their neonates, with an additional 6 months of efficacy during early infancy.[89–95] In addition, these safety data included comprehensive studies and monitoring programs for the adjuvant- and nonadjuvant-containing inactivated trivalent seasonal influenza vaccine and the H1N1 monovalent vaccines.[89–95] With support from the CDC, American Academy of Pediatrics, American Academy of Family Medicine, ACIP, and ACOG, a consensus statement was published, recommending that all women receive both the seasonal and 2009 H1N1 inactivated vaccines during pregnancy with FDA approval within 6 months from the start of the H1N1 pandemic.[109–112] These vaccines, along with known toxoids, have been used to prevent infectious morbidity known to negatively impact maternal and neonatal health.[109–113] For example, the administration of the seasonal and H1N1 influenza vaccine and tetanus toxoid vaccine (combined with diphtheria-pertussis, Tdap) has resulted in a 92% reported reduction in global pertussis morbidity and mortality.[113]

With the disclosure of full intent to perform future research on COVID-19 vaccine safety in this population, the DHHS, companies, and researchers prioritized the emergent delivery of a safe and effective vaccine to the public, responding to an emergent call to action, unfortunately with limited time and lower thresholds for evidence before implementation for the pregnant and lactating patient.[13–24,81]

Coronavirus Disease 2019 Vaccine and Pregnancy

Maternal risks and benefits

On December 19, 2020, the CDC and ACIP released a statement supporting the administration of both EUA-approved vaccines to prevent COVID-19 in persons aged ≥16 and 18 years, respectively, starting with prioritization groups outlined by the ACIP.[50,52,53] This strategy includes beginning with healthcare personnel and long-term care facility residents (Phase 1a), followed by persons aged ≥75 years and nonhealthcare frontline essential workers (Phase 1b), and in Phase 1c, the vaccines should be offered to persons aged 65 to 74 years, persons aged 16 to 64 years with high-risk medical conditions, and essential workers not included in Phase 1b.[50,52,53] In addition, the CDC, ACOG, SMFM, and other agencies support offering vaccination to pregnant and lactating women in these prioritized groups.[47–53] Counseling should include discussion of the risks and benefits for those contemplating vaccination before or during pregnancy or while breastfeeding with their trusted provider and support network. Mild side effects have been reported, ranging from a >80% frequency of pain at injection site to a 40% rate of systemic complaints, including febrile morbidity, which on review has been disproven to be teratogenic to the fetus during the first trimester of pregnancy.[114,115] Bell palsy affected few recipients of both Pfizer-BioNTech and Moderna vaccines but was not attributed to the vaccination.[16,18,21]

Counseling regarding anticipated benefits is clear, as published data reveal between 94% and 95% efficacy in preventing laboratory-confirmed and mildly symptomatic COVID-19 among people 7 to 14 days after completion of the vaccine series, with potential for similar efficacy for the pregnant patient based on similar efficacy observed between pregnant and nonpregnant individuals in other vaccine trials, regardless of pregnancy specifics.[13–21,81,96–109]

Major secondary endpoints of the BioNTech and Moderna COVID-19 vaccine studies include the efficacy of the vaccine against severe infection-related morbidity, defined by the FDA as confirmed COVID-19 with clinical signs that are indicative of severe systemic illness, including respiratory failure, evidence of shock, significant acute organ dysfunction, admission to an ICU, or death.[14–21] Although preliminary data report lower hospitalizations among vaccine recipients, these valuable data are not yet available and therefore cannot be fully addressed when counseling the pregnant patient concerned about these more serious outcomes or the potential reduction in the long-term sequelae of COVID-19 or risk of continued transmissibility.[14–21] If validated, a reduction in severe COVID-19 would benefit the fetus, given the negative effects maternal illness has on fetal status, which has driven medically indicated and spontaneous preterm birth and associated neonatal sequelae.[28–46] Counseling to this point can include a discussion of the continued pursuit and accumulation of pregnancy-specific COVID-19 data worldwide, with current data suggesting that rates of severe morbidity (assisted ventilation, ICU admission, and death) are significantly higher among pregnant women with symptomatic COVID-19 compared with symptomatic nonpregnant cohorts, respectively, which equally affect 5% of persons with infection.[35–46] However, when examining critical care details and demographic variables of pregnant women with infection in large national epidemiologic data, it remains critical to acknowledge that in the largest studies to date, the rates of ICU admission, invasive ventilation, and mortality from COVID-19 are 2- to 3-fold higher among symptomatic pregnant women over 35 years of age, with comorbidities (obesity, diabetes, cardiovascular disease, chronic lung disease), Black or Asian race or Hispanic ethnicity (Table 2).[35–46] These findings are further supported by a recent publication analyzing data from a national database encompassing 20% of hospitalizations in the United States, including women hospitalized for childbirth between April 1, 2020, and November 23, 2020.[46] Women with laboratory-confirmed COVID-19 along with obesity (body mass index of >35, kg/m^2) or diabetes or hypertensive disorders were significantly more likely to require

TABLE 2
ICU admissions, invasive ventilation, and deaths among symptomatic women of reproductive age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (N = 409,462)

Outcome or characteristic[a]	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Risk ratio (95% CI)
ICU admission[b]			
All	245 (10.5)	1492 (3.9)	3.0 (2.6–3.4)
Age group (y)			
25–34	118 (9.1)	467 (3.5)	2.4 (2.0–3.0)
35–44	78 (19.4)	781 (6.4)	3.2 (2.5–4.0)
Race and ethnicity			
Hispanic or Latina	89 (12.8)	429 (5.0)	2.8 (2.2–3.5)
Asian, non-Hispanic	20 (35.7)	52 (6.0)	6.6 (4.0–11.0)
Black, non-Hispanic	46 (13.6)	334 (6.2)	2.8 (2.0–3.8)
White, non-Hispanic	31 (5.6)	348 (2.8)	2.3 (1.6–3.3)
Underlying health conditions			
Diabetes	25 (58.5)	274 (44.8)	1.5 (1.0–2.2)
CVD[c]	13 (42.8)	247 (32.1)	1.5 (0.9–2.6)
Invasive ventilation[d]			
All	67 (2.9)	412 (1.1)	2.9 (2.2–3.8)
Age group (y)			
25–34	30 (2.3)	123 (0.9)	2.5 (1.6–3.7)[e]
35–44	26 (6.5)	221 (1.8)	3.6 (2.4–5.4)
Race and ethnicity			
Hispanic or Latina	33 (4.7)	143 (1.7)	3.0 (2.1–4.5)
Asian, non-Hispanic	4 (7.1)	19 (2.2)	NA
Black, non-Hispanic	10 (3)	86 (1.6)	2.5 (1.3–4.9)
White, non-Hispanic	12 (2.2)	102 (0.8)	3.0 (1.7–5.6)
Underlying health conditions			
Diabetes	10 (23.4)	98 (16.0)	1.7 (0.9–3.3)
CVD[c]	6 (19.7)	82 (10.6)	1.9 (0.8–4.5)[f]
Death[g]			
All	34 (1.5)	447 (1.2)	1.7 (1.2–2.4)
Age group (y)			
25–34	15 (1.2)	125 (0.9)	1.2 (0.7–2.1)
35–44	17 (4.2)	282 (2.3)	2.0 (1.2–3.2)
Race and ethnicity			
Hispanic or Latina	14 (2.0)	87 (1.0)	2.4 (1.3–4.3)
Asian, non-Hispanic	1 (1.8)	11 (1.3)	NA
Black, non-Hispanic	9 (2.7)	167 (3.1)	1.4 (0.7–2.7)
White, non-Hispanic	3 (0.5)	83 (0.7)	NA

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(continued)

TABLE 2
ICU admissions, invasive ventilation, and deaths among symptomatic women of reproductive age with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (N = 409,462) *(continued)*

Outcome or characteristic[a]	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Risk ratio (95% CI)
Underlying health conditions			
Diabetes	6 (14.1)	78 (12.7)	1.5 (0.6–3.5)[h]
CVD[c]	7 (23.0)	89 (11.6)	2.2 (1.0–4.8)[i]

Data are presented by pregnancy status, age, race, ethnicity, and comorbidities. Data for extracorporeal membrane oxygenation, multiple or other race, non-Hispanic, and unknown are included. Only adjusted risk ratio is included.

CI, confidence interval; *CVD*, cardiovascular disease; *ICU*, intensive care unit; *NA*, not available.

Adapted from Zambrano et al.[45]

[a] Percentages are based on the total number of pregnancies per status group: adjusted for age, categorical race and ethnicity variable, and dichotomous indicators for diabetes, CVD, and chronic lung disease; [b] A total of 17,007 (72.6%) symptomatic pregnant women and 291,539 (75.5%) symptomatic nonpregnant women were missing information on ICU admission status; [c] CVD accounts for the presence of hypertension; [d] A total of 17,903 (76.4%) pregnant women and 299,413 (77.6%) nonpregnant women were missing information regarding receipt of invasive ventilation and were assumed to have not received it; [e] Adjusted for presence of diabetes, CVD, and chronic lung disease only; data on race and ethnicity were from the adjustment set because of model convergence issues; [f] Adjusted for presence of diabetes and chronic lung disease and age as a continuous covariate only; data on race and ethnicity were removed from the adjustment set because of model convergence issues; [g] A total of 5152 (22.0%) pregnant women and 66,346 (17.2%) nonpregnant women were missing information on death and were assumed to have survived; [h] Adjusted for presence of CVD and chronic lung disease and age as a continuous variable; [i] Adjusted for presence of diabetes and chronic lung disease and age as a continuous variable.

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mechanical ventilation or die compared with women without those morbidities (odds ratio, 3.85 [95% CI, 2.05–7.21]; 4.51 [95% CI, 2.10–9.70]; 116.1 [95% CI, 22.91–588.50], respectively). Current data report that more than 21% of pregnant women with COVID-19 in the United States have been admitted to the hospital, but only 1.6% of women hospitalized for delivery between April 1, 2020, and November 23, 2020, were positive for COVID-19.[1–4,35–46] Overall, rates of severe morbidity among pregnant women remain low, with ICU admission approximating 3% and necessity for invasive ventilator support and death at 1.0 and 0.2%, respectively.[35–46] Even when symptomatic of COVID-19, these rates are substantially reduced to 0.9, 0.2, and 0.1%, respectively, in women less than 35 years of age without complicating health conditions.[45] In fact, according to current CDC surveillance data, mortality rates in persons less than 40 years of age is 0.0063%.[1–4]

Fetal risks and benefits

When balancing risks and benefits, it is important to clarify that there is no human trial demonstrating fetal and neonatal safety with the COVID-19 vaccines.[14–21] Furthermore, 36 pregnancies were reported among participants in the Pfizer-BioNTech and Moderna clinical trials combined, including 18 in the vaccine arms.[14–21] All pregnancy variables and outcomes, including any adverse safety events, will be recorded but are currently not available given the temporal relationship of these pregnancies and trial participation.[14–21]

Limited unpublished data are currently available from animal developmental and reproductive toxicity studies, which have revealed no safety concerns in over 1000 rats that received the Moderna COVID-19 vaccine before or during gestation with regard to female reproduction, fetal or embryonal, or postnatal development[17,18,47] Although human data surrounding detailed transplacental vaccine transfer, fetal teratogenicity, and immunogenicity are lacking, the administration of the vaccine does not seem to affect fertility or miscarriage rate in animal studies.[14–21,47,54,81] Because of the protection of passive immunoglobulins in preventing infectious morbidity for the neonate, certain vaccines are recommended by the ACOG, CDC, and ACIP for administration during pregnancy and in the third trimester of pregnancy (influenza, Tdap), a benefit that may or may not be revealed with longitudinal immunogenicity studies for the Pfizer-BioNTech and Moderna vaccines.[11,14–21,47–112]

Regarding lactation, it is worth noting that grouping pregnant and lactating women together in discussion of vaccine safety is neither helpful nor logical given that these phases of reproductive life are physiologically and biologically distinct. Experts (Academy of Breastfeeding Medicine, ACOG, etc.) agree that vaccination poses minimal to no potential risk to the newborn, given that vaccine-related mRNA has not been detected in early breast milk studies and no plausible mechanism of neonatal harm has been identified.[47–53,81] Based on the biology of other vaccines, there is the potential for neonatal benefit if vaccine-stimulated immunoglobulin A passes through breast milk and provides additional protection against SARS-CoV-2 infection.[47–53] Overall, safety for lactating women seems reassuring with no reason to suspect that receipt of the vaccine would lead to any adverse neonatal effects or harmful changes to lactation.[47–53]

Summary

In alignment with the current consensus statements and practice bulletin publications from the CDC, ACOG, SMFM, and other women's health organizations, we recognize that pregnant women meet the criteria as a prioritized group for administrating Pfizer-BioNTech and Moderna COVID-19 vaccines, especially for those with high-exposure occupations.[47–53] Importantly, for pregnant frontline workers currently eligible for the vaccination, efficacy and

TABLE 3
Recommended criteria for the administration of the currently available EUA-approved COVID-19 vaccines (BioNTech and Moderna COVID-19 vaccines) during pregnancy if one or more of the listed conditions is met using the Interim Clinical Considerations for use of the mRNA COVID-19 vaccines currently utilized in the United States

- Healthcare providers
- Women aged ≥35 y
- Multiple gestation
- Cancer
- Chronic hypertension
- Chronic kidney disease
- Chronic obstructive pulmonary disease
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Immunocompromised state (weakened immune system) from solid organ transplant
- Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graves' disease, psoriasis or psoriatic arthritis, Addison's disease
- Obesity (body mass index of 30 kg/m^2 or higher)
- Sickle cell disease
- Smoking (current or history)
- Type 1 or 2 diabetes mellitus

Contraindications: severe allergic reaction (eg, anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components.

Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including PEG).

Immediate allergic reaction of any severity to polysorbate (because of potential cross-reactive hypersensitivity with the vaccine ingredient (PEG).

COVID-19, coronavirus disease 2019; *EUA*, Emergency Use Administration; *PEG*, polyethylene glycol.

Adapted from the Centers for Disease Control and Prevention.[116]

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safety data will not be available in time to inform their decision-making. Pregnant women who choose to wait for more data should be supported and updated with evidence by their trusted healthcare provider. Overall, the benefits of the vaccine are promising. Nevertheless, risks and benefits of the COVID-19 vaccines for pregnant women, the fetus, and the newborn must be acknowledged in transparent discussions with our patients.[14–21,47–53] Fundamentally, the risks of neonatal transmission and overall infection-related morbidity and mortality in the low-risk pregnant patients presenting without symptoms are considerably reduced but are yet to be fully determined.[35–46]

In our expert opinion, we recommend a comprehensive risk-benefit discussion regarding the lack of safety data before COVID-19 vaccine administration in pregnant women with preferential administration for pregnant women at highest risk of more severe infection-related diseases until safety and efficacy of these novel COVID-19 vaccines are ensured (Table 3).[116] ■

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GLOSSARY OF TERMS

Advisory Committee on Immunization Practices	ACIP
Developmental and Reproductive Toxicology	DART
Emergency Use Authorization	EUA
Global Advisory Committee on Vaccine Safety	GACVS
National Institutes of Health	NIH
US Department of Health and Human Services	DHHS
Vaccine Safety Datalink	VSD
World Health Organization	WHO

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