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COVID-19 vaccination among pregnant people in the United States: a systematic review



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Introduction

Pregnant people are at increased risk of COVID-19–related morbidity and mortality. The heightened morbidities are noted in terms of an increased risk of preterm birth,^{1,2} increased need for intensive care unit (ICU) admission and invasive ventilation, and death.^{3–5} Vaccination presents an important strategy to prevent negative outcomes in this population. The Centers for Disease Control and Prevention, American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine recommend that pregnant people receive COVID-19 vaccines.^{6–8}

Because pregnant people were not included in the COVID-19 vaccine trials, there are limited data on vaccination

Cite this article as: Rawal S, Tackett RL, Stone RH, et al. COVID-19 vaccination among pregnant people in the United States: a systematic review. *Am J Obstet Gynecol MFM* 2022;4:100616.

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Received January 6, 2022; revised March 2, 2022; accepted March 7, 2022.

The authors report no conflict of interest.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The study was registered under the The International Prospective Register of Systematic Reviews (under registration number: CRD42021286726, registration date: November 01, 2021)

The abstract has been submitted to the upcoming meeting of The Professional Society for Health Economics and Outcomes Research 2022, to be held at National Harbor, MD, May 15–18, 2022.

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/\$36.00

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<http://dx.doi.org/10.1016/j.ajogmf.2022.100616>

OBJECTIVE: Pregnant people are at increased risk of COVID-19–related morbidity and mortality, and vaccination presents an important strategy for preventing negative outcomes. However, pregnant people were not included in vaccine trials, and there are limited data on COVID-19 vaccines during pregnancy. The objectives of this systematic review were to identify the safety, immunogenicity, effectiveness, and acceptance of COVID-19 vaccination among pregnant people in the United States.

DATA SOURCES: Four databases (PubMed, Web of Science, CINAHL, and Google Scholar) were used to identify eligible studies published from January 1, 2020 through February 6, 2022.

STUDY ELIGIBILITY CRITERIA: Inclusion criteria were peer-reviewed empirical research conducted in the United States, publications in English, and research addressing 1 of the following topics: safety, immunogenicity, effectiveness, and acceptance of COVID-19 vaccination among pregnant people.

METHODS: A narrative synthesis approach was used to synthesize findings. Critical appraisal was done using the JBI (formerly Joanna Briggs Institute) tool.

RESULTS: Thirty-two studies were identified. Most studies (n=24) reported the use of Pfizer and Moderna COVID-19 vaccines among pregnant people; only 6 reported the Janssen vaccine. Of the 32 studies, 11 examined COVID-19 vaccine safety, 10 investigated immunogenicity and effectiveness, and 11 assessed vaccine acceptance among pregnant people. Injection-site pain and fatigue were the most common adverse events. One case study reported immune thrombocytopenia. COVID-19 vaccination did not increase the risk of adverse pregnancy or neonatal outcomes compared with unvaccinated pregnant people. After COVID-19 vaccination, pregnant people had a robust immune response, and vaccinations conferred protective immunity to newborns through breast milk and placental transfer. COVID-19 vaccine acceptance was low among pregnant people in the United States. African American race, Hispanic ethnicity, younger age, low education, previous refusal of the influenza vaccine, and lack of provider counseling were associated with low vaccine acceptance.

CONCLUSION: Peer-reviewed studies support COVID-19 vaccine safety and protective effects on pregnant people and their newborns. Future studies that use rigorous methodologies and include diverse populations are needed to confirm current findings. In addition, targeted and tailored strategies are needed to improve vaccine acceptance, especially among minorities.

Key words: COVID-19 vaccine, immunogenicity, messenger RNA vaccine, neonatal outcomes, pregnancy, pregnancy outcomes, vaccine acceptance, vaccine effectiveness, vaccine hesitancy, vaccine safety

EDITOR'S CHOICE

safety and pregnancy outcomes compared with the general population.^{9,10} The lack of safety and efficacy data means that pregnant people are left with 2 options: get the vaccine, with limited safety and efficacy data, or skip the vaccine, thus leaving themselves and their fetuses vulnerable to adverse effects of COVID-19. Reviews of recent studies

indicate that COVID-19 vaccination during pregnancy produces immune responses and does not cause major adverse effects and negative pregnancy or neonatal outcomes.^{11,12} Although there has been exponential growth in research on COVID-19 vaccination during pregnancy, many of these reviews included vaccines that are not authorized in the United States.^{11,12} Furthermore, these reviews included studies

AJOG MFM at a Glance

Why was this study conducted?

Pregnant people are at increased risk of COVID-19–related morbidity and mortality. There are limited data regarding the safety, effectiveness, and acceptance of COVID-19 vaccination among pregnant people in the United States.

Key findings

Peer-reviewed studies support COVID-19 vaccines' safety and effectiveness in pregnant people and their fetuses or neonates; however, vaccine acceptance was low, especially among minorities.

What does this add to what is known?

This systematic review explored the safety, effectiveness, and acceptance of COVID-19 vaccination among pregnant people in the United States. The safety and effectiveness of the COVID-19 vaccine among pregnant people are similar to those reported in the general population. However, pregnant people exhibited vaccine hesitancy because of fear of vaccine side effects and risks to the fetus or neonate.

conducted in international settings where vaccine availability, vaccine guidelines, and healthcare systems differ from those of the United States. In addition, none of the reviews provided information about the acceptance and uptake of COVID-19 vaccines among pregnant people. Therefore, there is an urgent need for a clear understanding of the safety, efficacy, and acceptance of COVID-19 vaccination during pregnancy so that pregnant people may be supported in making the best decision for their individual situations.

Objective

The objective of this systematic review was to identify and synthesize what is known about COVID-19 vaccination among pregnant people in the United States, including safety, effectiveness, acceptance, hesitancy, and uptake.

Methods

The review protocol was registered with the International Prospective Register of Systematic Reviews under CRD42021286726 (at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=286726). The Population, Intervention, Comparison, and Outcome framework was used to organize this review.¹³ The population of interest was pregnant people in the United States. The intervention included COVID-19 vaccinations. The outcomes were safety,

immunogenicity, effectiveness, and acceptance of the COVID-19 vaccinations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to direct the methodology of this systematic review.¹⁴

Information sources and search strategy

A literature search was conducted to include studies published from January 1, 2020 through February 6, 2022. Sources included the following databases: PubMed, Web of Science, CINAHL, and Google Scholar. The key terms included in the search were “pregnant OR pregnancy OR pregnant women” and “COVID-19 vaccine OR COVID-19 vaccination.” Search results from each database were exported to EndNote (Clarivate, Philadelphia, PA). The full details of the search strategy are available in [Supplementary Table S1](#).

Study selection and data extraction

Studies were included if they were peer-reviewed empirical studies conducted in the United States from January 1, 2020 through February 6 2022, published in English, and addressed at least 1 of the following topics: (1) safety, immunogenicity, and effectiveness of COVID-19 vaccination in pregnant people or (2) attitudes, beliefs, perceptions, acceptance, or hesitancy of pregnant people toward COVID-19 vaccination. The

exclusion criteria included nonempirical and non–peer-reviewed research, studies published only as abstracts, literature reviews, commentaries, editorials, animal-model studies, studies not examining COVID-19 vaccination in pregnant people, studies published in non-English languages, and studies conducted outside the United States. Research conducted outside the United States was excluded because of the difference in vaccine availability, health advisories, and healthcare system structures. The 2-year time frame was used because the first case of COVID-19 was reported in the United States in January 2020, and vaccination began in December 2020.

Initial screening of all abstracts and titles was conducted by S.R. and checked by another author (H.N.Y.) to determine whether to include or exclude studies on the basis of the inclusion criteria. All full-text screening disagreements were reconciled through discussion between the authors (S.R., R.H.S., R.L.T., and H.N.Y.) to achieve mutual consensus before moving to full-text review.

Assessment of risk of bias

Critical appraisals of included studies were conducted to evaluate the methodological quality of research, that is, to what extent a study was designed, conducted, analyzed, interpreted, and reported to avoid systematic errors.¹⁵ Appraisals focused on methodological domains through which bias may have been introduced into the results.¹⁵ All studies identified as meeting the inclusion criteria were assessed for risk of bias by using the JBI (formerly Joanna Briggs Institute) critical appraisal checklist for cohort studies, case-control, case report, case series, quasi-experimental (prepost), and cross-sectional studies.¹⁶ The checklist response options included: “Yes” (the criteria are clearly identifiable through the report description), “Unclear” (the criteria are not clearly identified in the report), and “No” (the criteria are not identifiable). On the basis of the number (%) of “Yes” responses, the risk of bias was ranked as “high” ($\leq 49\%$), “moderate”

(50%–69%), and “low” ($\geq 70\%$).¹⁶ Two independent reviewers (S.R. and H.N. Y.) conducted the appraisals, and both reviewers were blinded to each other's quality appraisal reviews. After independent review, the results were collected by the first reviewer (S.R.), and discrepancies were discussed with a third reviewer (R.L.T.). There were no exclusions made on the basis of a minimum threshold.

Data synthesis

A standard data extraction form was used to collect the following information: study author(s) and year published, study title, study design, study setting, participants, COVID-19 vaccine type, outcomes, and conclusion(s). Data extraction and data synthesis were initially conducted by the first reviewer (S.R.) but discussed regularly with the review team (R.H.S., R.L.T., and H.N. Y.) to obtain agreement on all included studies and resolve any disagreements. A narrative synthesis approach was used to analyze studies included in this review.¹⁷ This approach synthesizes findings from multiple sources and primarily uses words and text to summarize and explain findings¹⁷; it is used when meta-analysis is not feasible because of high heterogeneity across studies.

Results

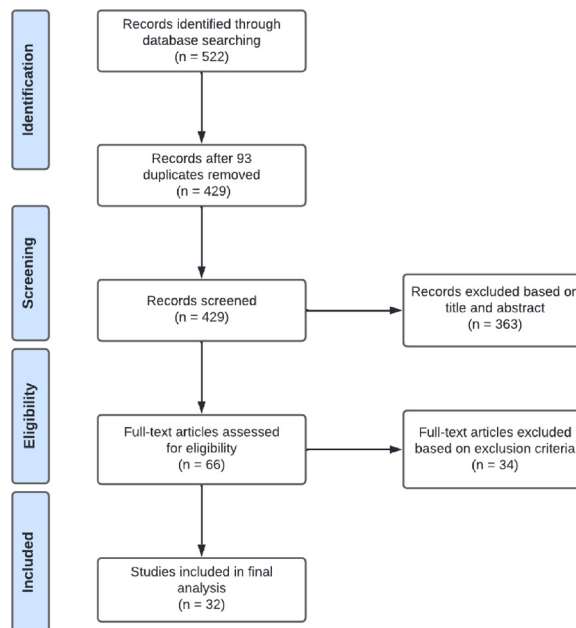
Study selection

A total of 522 studies were obtained from PubMed, Web of Science, and CINAHL and imported into EndNote software. Removal of 93 duplicates yielded 429 studies. Of those, 363 studies were removed on the basis of exclusion criteria during the title and abstract screening. The remaining 66 studies were screened for full-text review. Of these, 34 were excluded for not meeting the eligibility criteria. Therefore, 32 studies were included in the review (Figure 1).

Study characteristics

The characteristics of included studies are described in the Table 1. All of the included studies used observational study designs; there were 15 cohort, 10

FIGURE 1
PRISMA flow diagram of the included studies



The PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened, full texts retrieved, and the final studies included in the analysis.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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cross-sectional, 4 case report, 1 prepost, 1 case-control, and 1 case series study. No randomized controlled trials were identified. Seven studies used COVID-19 vaccination registries and had sample sizes ranging from 2002 to 135,968; the remaining 25 had sample sizes < 1030 . Twenty-four studies reported the use of Pfizer (Pfizer, Inc., New York, NY and BioNTech, Germany) and Moderna (ModernaTX, Inc.; Cambridge, MA) COVID-19 vaccines among pregnant people; 6 reported the Janssen (Janssen Biotech, Inc.; a Janssen Pharmaceutical Company of Johnson & Johnson, Horsham, PA) vaccine. Only 1 study reported the use of COVID-19 vaccine boosters in pregnant people. Five studies compared vaccinated pregnant people with vaccinated nonpregnant people, and 5 studies compared vaccinated pregnant people with unvaccinated pregnant people.

Risk of bias of included studies

Critical appraisals showed that 16 studies had a low risk of bias, 14 had

moderate risk, and 2 exhibited high risk. One case-control study included in this review did not match participants, and only 7 studies controlled for confounders. Three studies were purely descriptive, and 2 studies did not explain which statistical test was used to compare differences in observations before and after an intervention. Cross-sectional studies assessing vaccine acceptance did not use valid and reliable instruments to measure acceptance. Additional details regarding the risk of bias are summarized in Supplementary Tables S2 to S7.

Synthesis of results

COVID-19 vaccine safety. Eleven of the 32 (34%) studies (Figure 2) discussed COVID-19 vaccination–related side effects in pregnant people,^{18–20,23,25,32} pregnancy outcomes (gestational hypertension, preeclampsia, thromboembolism, placental injuries, miscarriage, and stillbirth),^{21,24–28} and neonatal outcomes (preterm birth, congenital

TABLE 1
Characteristics of included studies (n=32)

COVID-19 vaccine safety

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine types, % received	Outcomes	Conclusions
Bennett et al, ¹⁸ 2021	Newly diagnosed immune thrombocytopenia in a pregnant patient after coronavirus disease 2019 vaccination	Case report	Hospital in Ohio	Vaccinated pregnant woman at the first trimester of pregnancy (n=1)	Moderna mRNA-1273 Patient received first dose only.	Vaccine side effects: ITP occurred 13 d after COVID-19 vaccination. ITP was resolved by oral corticosteroids and patient was discharged on the fourth day of hospitalization with no complications.	COVID-19 vaccination benefits outweigh the risk of infection in pregnancy. Pregnant women should be included in clinical trials.
Kachikis et al, ¹⁹ 2021	Short-term reactions among pregnant and lactating individuals in the first wave of the COVID-19 vaccine rollout	Cohort study	Online registry in the United States	Pregnant (n=7809), lactating (n=6815), and neither pregnant nor lactating women planning pregnancy (n=2901)	Pfizer-BioNTech BNT162b2: 61.9% Moderna mRNA-1273: 37.8% Janssen JNJ-78436735: 0.23% 85.9% of all participants received both doses.	Vaccine side effects: Women who received vaccine experienced pain at injection site (91.4%) and fatigue (31.3%). Pregnancy outcomes: 0.7% of pregnant women reported miscarriages at the time of their second vaccine dose.	COVID-19 vaccines were well-tolerated among pregnant women.
Kadali et al, ²⁰ 2021	Adverse effects of COVID-19 messenger RNA vaccines among pregnant women: a cross-sectional study on healthcare workers with detailed self-reported symptoms	Cross-sectional survey	Online survey of US adults	Vaccinated pregnant HCWs (n=38) and nonpregnant HCWs (n=991)	Pfizer-BioNTech BNT162b2: 52.6% Moderna mRNA-1273: 47.4% About 31 of 38 (81.58%) of the pregnant HCWs received both doses of the mRNA vaccine.	Vaccine side effects: The vaccine side effects experienced by pregnant HCWs were minor and included sore arm (93%) and itching (5%). The side effects seemed to be similar (with no significant statistical difference) to those observed in nonpregnant HCWs.	COVID-19 vaccine side effects and safety were comparable between pregnant and nonpregnant HCWs.
Kharbanda et al, ²¹ 2021	Spontaneous abortion following COVID-19 vaccination during pregnancy	Case-control surveillance of Vaccine Safety Datalink	8 health systems (5 Kaiser Permanente health systems; Denver Health; HealthPartners; and Marshfield Clinic in Washington, California, Colorado, Wisconsin	Pregnant women (n=105,446)	Pfizer-BioNTech BNT162b2: received ≥1 doses (7.80%) Moderna mRNA-1273: received ≥1 doses (6.0%) Janssen JNJ-78436735: 0.50%	Pregnancy outcomes: A total of 13,160 miscarriages and 92,286 ongoing pregnancies were identified. Spontaneous abortions were not associated with increased odds of exposure to COVID-19 vaccine in the previous 28 d compared with ongoing pregnancies (aOR, 1.02; 95% CI, 0.96–1.08). Results were consistent for mRNA-1273 and BNT162b2 and by gestational age group.	Among women with miscarriages, the odds of COVID-19 vaccine exposure were not increased in the previous 28 d compared with women with ongoing pregnancies.
Lipkind et al, ²² 2022	Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth - eight integrated healthcare organizations, United States, December 15, 2020-July 22, 2021	Cohort study	8 health systems (5 Kaiser Permanente health systems; Denver Health; HealthPartners; and Marshfield Clinic in Washington, California, Colorado, Wisconsin	Unvaccinated pregnant women (n=36,015) and vaccinated pregnant women (n=10,064)	Pfizer-BioNTech BNT162b2: received ≥1 doses (54.40%) Moderna mRNA-1273: received ≥1 doses (41.40%) Janssen JNJ-78436735: 4.20%	Pregnancy outcomes: Prevalence of preterm birth and SGA neonates were 6.6 and 8.2/100 live births, respectively. COVID-19 vaccination during pregnancy was not significantly associated with increased risk for preterm birth overall (aHR, 0.91; 95% CI, 0.82–1.01; P=.06) or SGA neonates (aHR, 0.95; 95% CI, 0.87–1.03; P=.24).	COVID-19 vaccination during pregnancy is not associated with negative neonatal outcomes when compared with unvaccinated pregnant women.
Nakahara et al, ²³ 2022	Safety-related outcomes of novel mRNA COVID-19 vaccines in pregnancy	Cohort study	Ochsner Health System in Louisiana and Mississippi	Unvaccinated women (n=166) and vaccinated pregnant women (n=83)	mRNA vaccine (type not stated)	Pregnant individuals were more likely to report fever (4.80% vs 0.60%; P=.04) and gastrointestinal symptoms (4.80% vs 0%; P=.01). Frequency of complaint following vaccine administration was not different between pregnant and nonpregnant persons (18.10% vs 16.90%, P=.20).	Side effects following COVID-19 vaccination were similar between pregnant and nonpregnant individuals.

(continued)

TABLE 1

Characteristics of included studies (n=32) (continued)

COVID-19 vaccine safety

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine types, % received	Outcomes	Conclusions
Shanes et al, ²⁴ 2021	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in pregnancy	Cohort study	Hospital in Chicago	Unvaccinated pregnant (n=116) and vaccinated pregnant women (n=84)	mRNA vaccine (type not stated)	Pregnancy outcomes: Placental examination in vaccinated women showed no increased incidence of placental injuries compared with the control group.	There were no observed adverse pregnancy outcomes and placental injuries in vaccinated pregnant women.
Shimabukuro et al, ²⁵ 2021	Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons	Cohort study	COVID-19 Vaccine Pregnancy Registry in the United States	Vaccinated pregnant women (n=35,691)	Pfizer-BioNTech BNT162b2: 53.9% Moderna mRNA-1273: 46.10%	Vaccine side effects: Injection-site pain reported. Pregnancy outcomes: No neonatal deaths were reported. There were 12.60% of spontaneous abortions, 9.40% of preterm births, and 3.20% of SGA neonates.	Preliminary findings did not show any major safety issues among pregnant mRNA vaccine recipients.
Theiler et al, ²⁶ 2021	Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy	Cohort study	Mayo Clinic Health System in Minnesota and Wisconsin	Unvaccinated pregnant women (n=1862) and vaccinated pregnant women (n=140)	Pfizer-BioNTech BNT162b2: 90.70% Moderna mRNA-1273: 8.57% Janssen JNJ-78436735: 0.71% 73.60% of pregnant women completed both doses of vaccination before delivery.	Pregnancy outcomes: Thromboembolic events, gestational hypertension, and preeclampsia risk were similar between vaccinated and unvaccinated pregnant women. Neonatal outcomes: Preterm birth and neonatal birthweight in pregnant vaccinated people were similar to those of unvaccinated pregnant women.	Vaccinated pregnant women were less likely to experience COVID-19 infection than unvaccinated pregnant women. Vaccination during pregnancy was not associated with increased pregnancy or delivery complications.
Trostle et al, ²⁷ 2021	COVID-19 vaccination in pregnancy: early experience from a single institution	Cohort study	Academic medical center in New York	Vaccinated pregnant women (n=424)	mRNA vaccine: 100%. Of those, 82.10% received both doses and 17.90% received only 1 dose.	Pregnancy outcomes: Nine women had spontaneous abortions, 3 terminated their pregnancies, and 327 had ongoing pregnancies. There were no stillbirths. Neonatal outcomes: The rate of preterm birth was 5.90%. There were 15.30% of neonates requiring admission to the NICU. Amount of SGA neonates (per WHO standards) was 12.20%.	The rate of spontaneous abortion in this study was within the expected rate of 10%, and preterm birth rate of 5.9% was below the national average of 9.50%. The 12.20% rate of SGA neonates was near the expected value.
Zauche et al, ²⁸ 2021	Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion	Cohort study	COVID-19 vaccine pregnancy registry in the United States	Vaccinated pregnant women (n=2456)	Pfizer-BioNTech BNT162b2: 52.70% Moderna mRNA-1273: 47.30%	Pregnancy outcomes: The cumulative risk of spontaneous abortion from 6 to <20 wk of gestation was 14.10% (95% CI, 12.10–16.10) in the primary analysis and 12.80% (95% CI, 10.80–14.80) in an analysis using direct maternal age standardization to the reference population.	The risk of spontaneous abortion after mRNA COVID-19 vaccination is consistent with the expected risk of spontaneous abortion. The mRNA COVID-19 vaccination is safe in pregnancy.

COVID-19 vaccine immunogenicity and effectiveness

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine type, % received	Outcomes	Conclusions
Ateyo et al, ²⁹ 2021	COVID-19 mRNA vaccines drive differential antibody Fc-functional profiles in pregnant, lactating, and nonpregnant women	Cohort study	Tertiary care centers in the United States	Vaccinated, pregnant (n=84), lactating (n=31), and nonpregnant (n=16) age-matched controls	Both doses of Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273	Vaccine-specific antibody levels were lower than those of nonpregnant women after the first vaccine dose, which normalized after the second dose.	There is a need to administer both doses of the COVID-19 vaccine in pregnant people to ensure full immunity is attained.

(continued)

TABLE 1
Characteristics of included studies (n=32) (continued)

COVID-19 vaccine immunogenicity and effectiveness

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine type, % received	Outcomes	Conclusions
Collier et al, ³⁰ 2021	Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women	Cohort study	Hospital in Massachusetts	Pregnant (n=30), lactating (n=16), and neither pregnant nor lactating women (n=57) who were vaccinated or had had confirmed COVID-19 infection in the past	Both doses of Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273	Pregnant, lactating, and nonpregnant women who were vaccinated developed antibody responses and T-cell responses against COVID-19 infection.	Pregnant and nonpregnant vaccinated women developed antibody responses and T-cell responses against SARS-CoV-2 variants.
Gill and Jones, ³¹ 2021	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in neonatal cord blood after vaccination in pregnancy	Case study	Hospital in Minnesota	Pregnant woman vaccinated in the third trimester of pregnancy (n=1)	Both doses of Pfizer-BioNTech BNT162b2 mRNA vaccine	Uncomplicated spontaneous vaginal delivery of a female neonate occurred at term. The patient's blood and neonatal cord blood were evaluated for SARS-CoV-2-specific antibodies. Both the patient and the neonate were positive for antibodies. There was transplacental transfer of neutralizing SARS-CoV-2 antibodies.	This is the first case report documenting transplacental transfer of neutralizing SARS-CoV-2 antibodies after vaccination in the third trimester of pregnancy.
Gray et al, ³² 2021	Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study	Cohort study	Academic medical centers in Massachusetts	Vaccinated pregnant (n=84), lactating (n=31), and nonpregnant women (n=16)	Pfizer-BioNTech BNT162b2: 49% Moderna mRNA-1273: 51%	Vaccines created robust humoral immunity in pregnant and lactating women, with immunogenicity similar to that of nonpregnant women (pregnant: median, 5.59; IQR, 4.68–5.89; lactating: median, 5.74; IQR, 5.06–6.22; nonpregnant: median, 5.62; IQR, 4.77–5.98; <i>P</i> =.24). Vaccine-generated antibodies were present in all umbilical cord blood and breast milk samples.	COVID-19 mRNA vaccines generated immunity in pregnant and lactating women, with immunogenicity similar to that observed in nonpregnant women. Immune transfer to neonates occurred via placental transfer and breast milk.
Mangat and Milosavljevic, ³³ 2021	BNT162b2 vaccination during pregnancy protects both the mother and infant: anti-SARS-CoV-2 S antibodies persistently positive in an infant at 6 months of age	Case study	Mayo Clinic Health System	Pregnant woman vaccinated with 2 doses of COVID-19 vaccine at 22 and 26 wk of gestation (n=1)	Both doses of Pfizer-BioNTech BNT162b2 mRNA vaccine	At 33 wk of gestation, a preterm neonate was delivered via emergency cesarean delivery. To evaluate for SARS-CoV-2-specific antibodies, a serologic test was done on the newborn at 6 wk, 3 mo, and 6 mo. Positive anti-SARS-CoV-2 S antibodies were detected in the infant at 6 wk, 3 mo, and 6 mo of age.	There was transplacental transfer of neutralizing SARS-CoV-2 antibodies after vaccination during pregnancy, and the immune response persisted at the infant's 6 mo of age.
Mithal et al, ³⁴ 2021	Cord blood antibodies following maternal coronavirus disease 2019 vaccination during pregnancy	Case series	Hospital in Chicago	Vaccinated pregnant women (n=27)	Pfizer-BioNTech BNT162b2: 64% Moderna mRNA-1273: 18% Unknown: 14%	Maternal plasma and cord blood testing showed that 96.29% had a positive SARS-CoV-2 IgG test at the time of delivery. Of 28 neonates, 25 had positive IgG tests. The observed mean IgG transfer ratio demonstrated that infant antibody levels were about equal to the maternal levels.	Pregnant women who received a COVID-19 mRNA vaccine during the third trimester had transplacental transfer of IgG to the infant.
Paul and Chad, ³⁵ 2021	Newborn antibodies to SARS-CoV-2 detected in cord blood after maternal vaccination - a case report	Case study	Hospital in Florida	Vaccinated pregnant woman (n=1)	Single dose of Moderna mRNA-1273	COVID-19-naïve mother who had received a single dose of mRNA vaccine 3 wk before delivery delivered an infant with SARS-CoV-2 IgG antibodies detectable in cord blood.	SARS-CoV-2 IgG antibodies are detectable in a newborn's cord blood sample after only a single dose of the Moderna vaccine. Thus, there is potential for protection and infection risk reduction from SARS-CoV-2 with maternal vaccination.

(continued)

TABLE 1

Characteristics of included studies (n=32) (continued)

COVID-19 vaccine immunogenicity and effectiveness

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine type, % received	Outcomes	Conclusions
Prabhu et al, ³⁶ 2021	Antibody response to coronavirus disease 2019 (COVID-19) messenger rna vaccination in pregnant women and transplacental passage into cord blood	Cross-sectional study	Academic medical center in New York	Vaccinated pregnant women (n=122)	Pfizer-BioNTech BNT162b2: 69.67% Moderna mRNA-1273: 30.32% Single dose of the COVID-19 vaccine received by 55 and both doses by 67 participants.	Cord blood testing of vaccinated pregnant women showed antibody production. Maternal antibody production started on the 5th day and transfer of immunity to the neonate on the 16th day after first vaccination. Maternal IgG-level increment was statistically significant. The association of maternal IgG levels with cord blood IgG levels was also statistically significant.	Pregnant women who received a COVID-19 mRNA vaccine had an immune response, and there was transplacental transfer of IgG to the neonate.
Trostle et al, ³⁷ 2021	High antibody levels in cord blood from pregnant women vaccinated against COVID-19	Cohort study	Academic medical center in New York	Vaccinated pregnant women (n=36)	Pfizer-BioNTech BNT162b2: 72% Moderna mRNA-1273: 28%	Cord blood testing after delivery showed transplacental antibody transfer, with cord blood specimens having high levels of anti-S antibodies.	COVID-19 vaccination during pregnancy confers high levels of antibody transfer in the neonates, suggesting immune protection against SARS-CoV-2.
Yang et al, ³⁸ 2021	Association of gestational age at COVID-19 vaccination, history of sars-cov-2 infection, and a vaccine booster dose with maternal and umbilical cord antibody levels at delivery	Cohort study	Medical center in New York	Vaccinated pregnant women (n=1359)	Pfizer-BioNTech BNT162b2: 75.42% Booster: 1.80% Moderna mRNA-1273: 22.15% Janssen JNJ-78436735: 2.43% Booster: 0.70%	The highest maternal and umbilical cord blood IgG antibody levels occurred with early-third-trimester vaccination. However, neonates born to women fully vaccinated early in the first trimester had similar or higher cord IgG levels than neonates born to women who were vaccinated in the third trimester but not fully vaccinated before delivery.	A complete COVID-19 vaccination course and a third-trimester booster dose were associated with the highest maternal and umbilical cord antibody levels.

COVID-19 vaccine acceptance

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine types, % received	Outcomes	Conclusions
Ahlers-Schmidt et al, ³⁹ 2020	Concerns of women regarding pregnancy and childbirth during the COVID-19 pandemic	Cohort study	Sedgwick County prenatal programs in Kansas	Pregnant (n=46) and postpartum women (n=68) enrolled in prenatal programs	Not stated	Vaccine acceptance: If a COVID-19 vaccine became available, 47.80% (n=54) were interested in receiving it, 23% were not, and 29.20% were unsure. Concerns were side effects/sickness (55.90%), cost (5.10%), and the perception of it being unnecessary (3.40%).	More than half of the participants would not receive or were unsure of receiving COVID-19 vaccination.
Battarbee et al, ⁴⁰ 2022	Attitudes toward COVID-19 illness and COVID-19 vaccination among pregnant women: a cross-sectional multicenter study during August-December 2020	Cross-sectional survey study	Salt Lake City, UT; Birmingham, AL; and New York, NY	Pregnant women (n=915)	Not stated	Vaccine acceptance: 41% of pregnant women were willing to get a COVID-19 vaccine. The major concern was vaccine safety (82%). Receipt of the influenza vaccine in the past year was associated with higher odds of vaccine acceptance (aOR, 2.10; 95% CI, 1.50–3.00). Black and Hispanic women had lower odds of accepting a vaccine than White women (aOR, 0.40; 95% CI, 0.20–0.60 for both).	More than half of the pregnant participants were unwilling to receive vaccination. Minorities and those without previous influenza vaccination were less likely to accept the COVID-19 vaccine.

(continued)

TABLE 1
Characteristics of included studies (n=32) (continued)

COVID-19 vaccine acceptance							
Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine types, % received	Outcomes	Conclusions
Desai et al, ⁴¹ 2021	COVID-19 vaccine acceptance in pregnancy	Cross-sectional survey study	Perinatal Center at the Pomona Valley Hospital in California	Pregnant women (n=124)	Not stated	Vaccine uptake: Pregnant women who had received the annual influenza vaccine were significantly more likely to get the COVID-19 vaccine (50% vs 9.70%; $P<.05$). Those who had previously discussed the COVID-19 vaccine with a physician were significantly more likely to receive the vaccine (45.80% vs 26%; $P=.04$).	Pregnant women who discussed the COVID-19 vaccine with a healthcare provider were statistically more willing to receive the vaccine.
Hirshberg et al, ⁴² 2021	Offering on-site COVID-19 vaccination to high-risk obstetrical patients: initial findings	Prepost study	Obstetrical clinic at a single academic medical center in Missouri and Illinois	High-risk obstetrical patients (n=93)	Pfizer-BioNTech BNT162b2 vaccine	Vaccine uptake: Of 32 eligible patients counseled before on-site vaccine availability, 1 (3%) received vaccination off-site. Of 55 eligible patients counseled after on-site vaccine availability, 2 (3%) received on-site vaccination, and 4 (7%) proceeded with vaccination off-site. On-site vaccination availability did not significantly increase vaccination rates (3% vs 11%; $P=.22$).	Vaccine hesitancy, not availability, is a critical driver of low vaccination rates in high-risk obstetrical patients.
Huddleston et al, ⁴³ 2021	COVID-19 vaccination patterns and attitudes among american pregnant individuals	Cross-sectional survey study	Online survey of US pregnant women	Pregnant women at <10 weeks' gestation (n=2506)	Not stated	Vaccine acceptance: Among the unvaccinated, only 35.70% reported vaccine acceptance. Predictors of lower odds of vaccination were Black race and being counseled not to vaccinate by a provider.	There was substantial vaccine hesitancy among unvaccinated respondents.
Levy et al, ⁴⁴ 2021	Acceptance of COVID-19 vaccination in pregnancy: a survey study	Cross-sectional survey study	Single ultrasound unit in New York	Pregnant women (n=653)	Not stated	Vaccine acceptance: 58.30% of pregnant women reported vaccine acceptance. Among those who declined vaccination, common concerns were risk to the fetus or neonate (45.80%) and vaccine side effects (17.70%). African American race, Hispanic ethnicity, low education, and declining the influenza vaccine were associated with nonacceptance of COVID-19 vaccination in pregnancy.	The COVID-19 vaccine acceptance rate of 58.4% was consistent with the acceptance of other recommended vaccines in pregnancy (DTaP, influenza) and is associated with patient characteristics and vaccine history.
Razzaghi et al, ⁴⁵ 2021	COVID-19 vaccination coverage among pregnant women during pregnancy — eight integrated healthcare organizations, United States, December 14, 2020—May 8, 2021	Cohort study	8 health systems (5 Kaiser Permanente health systems; Denver Health; HealthPartners; and Marshfield Clinic in Washington, California, Colorado, Wisconsin	Total population in the registry (N=135,968) Pregnant women who received ≥ 1 dose of COVID-19 vaccination during pregnancy (n=22,197)	Pfizer-BioNTech BNT162b2: 8.7% Moderna mRNA-1273: 7.0% Janssen JNJ-78436735: 0.6%	Vaccine uptake: 16.3% of pregnant women identified in CDC's Vaccine Safety Datalink had received ≥ 1 dose of a COVID-19 vaccine during pregnancy. Vaccination was lowest among Hispanic (11.90%), Black (6%), and women aged 18–24 y (5.50%). Concerns were limited safety data in pregnancy and possibility of harm to the fetus.	COVID-19 vaccination coverage is low among pregnant women.
Sutton et al, ⁴⁶ 2021	COVID-19 vaccine acceptance among pregnant, breastfeeding, and nonpregnant reproductive-aged women	Cross-sectional online survey study	Healthcare institution in New York	Pregnant (n=216), nonpregnant (n=656), and breastfeeding women (n=122) (including patients, providers, and staff) at a healthcare institution	Not stated	Vaccine acceptance: Pregnant women had the lowest rate of vaccine acceptance (44.30%; $P<.05$) compared with other groups. Nonpregnant women were most likely to accept vaccination (n=457, 76.20%; $P<.05$), with breastfeeding women being the second most likely (55.20%). Working in healthcare was not associated with vaccine acceptance.	Pregnant respondents were more likely to decline vaccination than nonpregnant and breastfeeding women.

(continued)

TABLE 1

Characteristics of included studies (n=32) (continued)

COVID-19 vaccine acceptance

Author(s), year	Study title	Study design	Study setting	Participants (n)	COVID-19 vaccine types, % received	Outcomes	Conclusions
Sznajder et al, ⁴⁷ 2022	Covid-19 vaccine acceptance and associated factors among pregnant women in Pennsylvania 2020	Cross-sectional online survey study	Academic medical center in Pennsylvania	Pregnant women (n=196)	Not stated	Vaccine acceptance: 65% of pregnant respondents were willing to receive the COVID-19 vaccine. Being employed full-time (aOR, 2.22; 95% CI, 1.02–4.81), being overloaded/stressed (aOR, 2.18; 95% CI, 1.02–4.68), and having had an influenza vaccine in the past year (aOR, 4.82; 95% CI, 2.17–10.72) were significantly associated with COVID-19 vaccine acceptance.	Factors associated with COVID-19 vaccine acceptance included having had an influenza vaccine in the previous year, being employed full-time, and a general feeling of being overloaded.
Townsel et al, ⁴⁸ 2021	COVID-19 vaccine hesitancy among reproductive-aged female tier 1A healthcare workers in a United States Medical Center	Cross-sectional online survey study	Academic medical center in Michigan	Pregnant (n=245), TTC (n=891), and breastfeeding (n=177) female employees at a medical center	Not stated	Vaccine acceptance: Pregnant participants were 6 times more likely to delay and twice as likely to decline COVID-19 vaccination ($P<.05$) compared with other women of reproductive age. The highest rates of concern were observed for safety and effectiveness of the vaccine.	Pregnant women had significantly higher rates of declining or delaying COVID-19 vaccination than other women of reproductive age.
Wang et al, ⁴⁹ 2022	Perceptions and knowledge of COVID-19 vaccine safety and efficacy among vaccinated and nonvaccinated obstetrical healthcare workers	Cross-sectional online survey study	Tertiary care institution in Pennsylvania	Vaccinated pregnant HCWs (n=65) and nonvaccinated pregnant HCWs (n=18)	At least 1 dose of Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273: 78.30%	Vaccine acceptance: Vaccine receipt was 16.90%. Pregnancy status influenced 8/18 (44.4%) nonvaccinated HCWs to not receive the COVID-19 vaccine, but influenced 1/65 (1.50%) vaccinated HCWs to receive the vaccine.	Pregnancy status, especially the uncertainty of COVID-19 vaccination safety in pregnancy, was a major reason for vaccine refusal among nonvaccinated HCWs.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DtaP, diphtheria, tetanus, and acellular pertussis; HCW, healthcare worker; IgG, immunoglobulin G; IQR, interquartile range; ITP, immune thrombocytopenia; mRNA, messenger RNA; NICU, neonatal intensive care unit; SGA, small for gestational age; TTC, trying to conceive; WHO, World Health Organization.

Rawal. COVID-19 vaccination among pregnant people in the United States. *Am J Obstet Gynecol MFM* 2022.

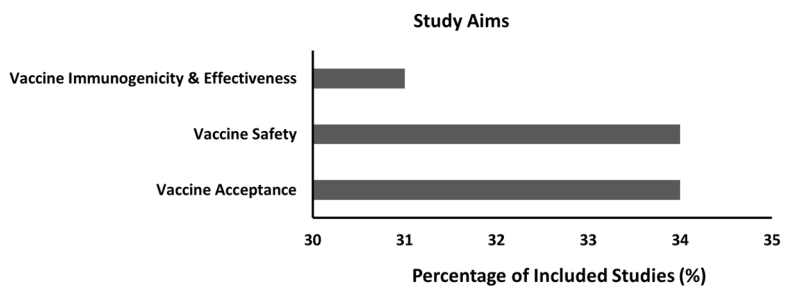
anomalies, small size for gestational age, neonatal ICU admission, and neonatal death).^{22,25–27}

Included studies that evaluated pregnancy and neonatal outcomes following COVID-19 vaccination did not demonstrate harmful effects with respect to pregnancy,^{21,24–28} fetal development,^{25–27} or neonatal outcomes.^{22,25–27} There were no statistical differences in pregnancy outcomes such as gestational hypertension ($P=60$), preeclampsia ($P=1.00$), and thromboembolism incidence ($P=1.00$) between vaccinated and unvaccinated pregnant people.²⁶ There were no placental injuries²⁴ and no stillbirths.^{26,27} The miscarriage rates after receiving COVID-19 vaccination ranged from 6.50% to 14.10%,^{25,27,28} similarly to the 11% to 16% expected rate of miscarriage in the general population.^{50,51} With respect to newborns, there was no increased risk of adverse neonatal outcomes because of COVID-19 vaccination during pregnancy. No neonatal deaths were reported in the included studies.^{25–27} Rates of other neonatal outcomes including preterm birth (9.40%, 5.90%),^{22,25,27} congenital anomalies (2.20%, 1.20%),^{25,27} small size for gestational age (3.20%, 12.20%),^{22,25,27} and neonatal ICU admission (0.70%, 15.30%)^{26,27} following COVID-19 vaccination were similar to the expected rates of neonatal outcomes in the unvaccinated population.^{52–56}

Side effects reported in pregnant people were similar to those observed in the general population, and the most common side effects included injection-site pain,^{19,20,25} injection-site soreness,^{20,21} fevers or chills,^{19,20,25,32} fatigue,^{19,20} and itching.²⁰ Immune thrombocytopenia (ITP) was reported in a case study.¹⁸ Studies showed that the incidence of side effects (injection-site pain, injection-site soreness, and fatigue) was higher with the second dose of vaccination than with the first dose.^{19,25,32}

COVID-19 vaccine immunogenicity and effectiveness. Ten of the 32 (31%) studies (Figure 2) in pregnant people examined the immunogenicity or the ability

FIGURE 2
Study aims and percentage of included studies



Rawal. COVID-19 vaccination among pregnant people in the United States. *Am J Obstet Gynecol MFM* 2022.

of the COVID-19 vaccine to elicit an immune response.^{32,26,30,31,33–44} These studies demonstrated that COVID-19 vaccination during pregnancy produced a robust immune response, and the antibody production was similar to that of nonpregnant people.^{30,32} These antibodies were also found in umbilical cord blood,^{32–38} which means COVID-19 vaccination during pregnancy may convey some immunity to neonates against COVID-19. In addition, the highest maternal and umbilical cord antibody levels were achieved through the completion of a full vaccination series and a booster dose.³⁸

Regarding the strength of the vaccine, immunity produced by the COVID-19 vaccination was found to be significantly stronger than that obtained after natural infection with the virus ($P<.05$).³² There was a rapid immunologic response following the first dose of the vaccine, and administration of the second dose further increased the antibody level among vaccinated pregnant people.³² Similar results were observed in an age-matched cohort study where pregnant people had lower antibody levels after the first dose, but by follow-up after the second dose, the achieved immune responses were comparable to those of nonpregnant people.²⁹ With regard to effectiveness, COVID-19 vaccination was effective in preventing COVID-19 infection among pregnant people. A study showed that only 9 of 2136 (0.40%) and 3 of 1822 (0.20%) pregnant people experienced COVID-

19 infection >14 days after the first Pfizer-BioNTech and Moderna vaccine, respectively.²⁵ Another study that compared vaccinated and unvaccinated pregnant people showed that vaccination significantly reduced the risk of future COVID-19 infection ($P<.05$).²⁶

COVID-19 vaccine acceptance. Eleven of the 32 (34%) studies (Figure 2) examined pregnant people's acceptance or uptake of COVID-19 vaccination.^{39–49} Overall, COVID-19 vaccine acceptance rates ranged between 3% and 65%. Studies conducted before the COVID-19 vaccine became available in the United States showed that 41%⁴⁰ and 47.80%³⁹ of pregnant people would be interested in receiving it. Vaccine-hesitant pregnant people had concerns about side effects, sickness, allergy to the vaccine, and a perception that the vaccine is unnecessary.³⁹ A study reported 65% vaccine acceptance among pregnant people; this study had a sample consisting of people with higher education and greater income⁴⁷ compared with other studies.^{39,43,44} The vaccine acceptance rate did not improve after the COVID-19 vaccine became available in the United States. Studies conducted after the vaccine became available showed acceptance rates of 3%,⁴² 16.30%,⁴⁵ 35.70%,⁴³ 44.30%,⁴⁶ and 58.30%.⁴⁴

Seven of the 11 vaccine acceptance studies examined factors that were associated with vaccine acceptance. Pregnant people's receipt of the influenza

vaccine in the previous year and communication with a medical professional about vaccines were associated with increased likelihood of COVID-19 vaccine acceptance.^{29,41,47} In contrast, pregnant people's previous refusal of the seasonal influenza vaccine,^{40,44} lack of provider counseling,⁴³ younger age,^{29,45} African American race,^{40,43–45,48} Hispanic ethnicity,^{40,43–45} and low education⁴³ were associated with refusal of vaccination. Frequently cited concerns included safety and effectiveness of COVID-19 vaccination, fears of birth defects, unknown long-term health effects on children, and risk of pregnancy loss.^{44,48,49}

Comment

Principal findings

This study reviewed the available literature on COVID-19 vaccination among pregnant people in the United States. Peer-reviewed observational studies support the assertion that the COVID-19 vaccine is safe during pregnancy and provides protective effects for both pregnant people and their newborns. Most of the reported side effects such as injection-site pain, soreness, fever or chills, and fatigue were not severe and were similar to those reported in the general population. ITP was reported in 1 case study.¹⁸ This very rare event has an incidence ranging from 1 case per 26,000 to 1 case per 127,000 doses,⁵⁷ and may be resolved by oral corticosteroids without subsequent complications.¹⁸

The protective effects of COVID-19 vaccines in pregnant people were similar to those observed in the general population. Pregnant people had a robust immune response after vaccination, with immunogenicity equivalent to that observed in nonpregnant people.³² The vaccines also conferred protective immunity to newborns through breast milk and placental transfer.^{27,32,35} This demonstrates that COVID-19 vaccination in pregnancy likely has a dual benefit: both the mother and newborn receive antibodies. Supported by studies that demonstrated the efficient maternal-fetal transplacental transfer of anti-COVID-19 antibodies,^{58,59} Israel placed pregnant people on its vaccine

priority list.⁶⁰ The United States has not formally prioritized COVID-19 vaccination for pregnant people, which may ultimately contribute to poorer maternal and fetal outcomes in the United States. Even though COVID-19 vaccination is beneficial during both pregnancy and lactation, it may be most beneficial during pregnancy because higher levels of antibodies were found in early milk than in later milk.³⁰

Although randomized controlled clinical trials involving pregnant people are lacking, data from all observational studies indicate that pregnant people tolerate COVID-19 vaccines well. Major adverse events have not been reported for mothers and fetuses or neonates, and the scientific understanding of the vaccine's mechanism of action does not raise theoretical safety concerns.^{21,25,28,45} Studies of COVID-19 vaccines authorized in the United States show that the vaccine virus does not cross the placenta.^{34,59} Only protective antibodies produced in the vaccinated mother's body are transferred to the neonates through breast milk or placental transfer.^{32,35,37} COVID-19 vaccine safety and effectiveness are important factors in achieving population immunity; however, wider acceptance of vaccines is crucial for achieving sufficient immunization coverage.

Current research indicates a low acceptance of COVID-19 vaccination among pregnant people in the United States. Specifically, Black and Latinx people have shown less trust in the vaccine, citing fear of side effects and risks to the fetus or neonate.^{39,44,48,49} The lack of trust in the COVID-19 vaccine and vaccine refusal may stem from long-standing medical distrust among various communities caused by historic misdeeds (eg, the Tuskegee Syphilis Study).⁶¹ Contemporary healthcare encounters may also cultivate distrust of healthcare professionals and researchers. A 2020 Kaiser Family Foundation survey of 1700 US adults showed that 45% of Black patients reported at least 1 of 6 types of negative experiences with a healthcare professional, and 36% believed they would have received better care if they were of different race or ethnicity.⁶²

Low acceptance of vaccines could be addressed by forming partnerships between healthcare and trusted

community-based organizations (CBOs). Collaborations with trusted CBOs can contribute to developing and delivering accurate, consistent, and transparent messaging to effectively promote vaccine acceptance and other positive health behaviors.^{63–65} Virtual town hall meetings hosted by community leaders and local healthcare providers (HCPs) can engage communities in discussions regarding COVID-19 vaccines.⁶⁶ Targeted messages conveyed through multiple languages that focus on vaccine safety, efficacy, and vaccines' ability to confer protective immunity to neonates may alleviate fear and increase the likelihood of vaccination.⁶⁷ HCPs discussing risk and benefit information with pregnant people during routine visits may be another strategy to alleviate fear and reduce vaccine hesitancy. Previous research has shown that vaccine communication comprising education and recommendations from HCPs bolstered Tdap and influenza vaccine acceptance among pregnant people.⁶⁸ Given what is known about COVID-19 vaccine safety and effectiveness, HCPs can use available data to educate and empower pregnant people to make informed decisions. In addition, HCPs who have received the COVID-19 vaccine when they were pregnant may be positioned to share their credible vaccination experiences. A national recommendation endorsing COVID-19 vaccine administration during pregnancy, with additional support and reinforcement by HCPs, may improve vaccine uptake by pregnant people.

Strengths and limitations

This systematic review explored COVID-19 vaccination among pregnant people in the United States and included all peer-reviewed empirical studies published so far on this topic. However, certain limitations of the present study should be acknowledged. First, all studies included in this review were observational, nonrandomized, and lacked long-term safety and effectiveness data. Thus, the evidence presented in this review may be limited because of previous study designs. Second, studies included

in this review were not excluded on the basis of critical appraisals of the research (ie, risk-of-bias assessments). It was considered important to include all studies irrespective of the risk of bias to obtain a more comprehensive picture of relevant research pertaining to the aim of this review. However, it is acknowledged that the lack of a minimum threshold may hold some limitations for the findings. Lastly, the evidence presented in this review may be limited for the Janssen COVID-19 vaccine, given that only 6 studies reported the use of the Janssen COVID-19 vaccine among pregnant people.

Conclusions and implications

Peer-reviewed studies support COVID-19 vaccine safety and protective effects on pregnant people and their newborns. Future studies that use rigorous methodologies and include diverse populations (eg, minorities and rural residents) are needed to confirm current findings and examine the effectiveness of COVID-19 vaccines and boosters against emerging SARS-CoV-2 variants during pregnancy. In addition, targeted and tailored strategies may help improve vaccine acceptance among pregnant people, especially vulnerable populations. ■

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ajogmf.2022.100616](https://doi.org/10.1016/j.ajogmf.2022.100616).

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