

Covid-19 vaccination in pregnancy

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

Abstract

Pregnancy is an independent risk factor for severe covid-19. Vaccination is the best way to reduce the risk for SARS-CoV-2 infection and limit its morbidity and mortality. The current recommendations from the World Health Organization, Centers for Disease Control and Prevention, and professional organizations are for pregnant, postpartum, and lactating women to receive covid-19 vaccination. Pregnancy specific considerations involve potential effects of vaccination on fetal development, placental transfer of antibodies, and safety of maternal vaccination. Although pregnancy was an exclusion criterion in initial clinical trials of covid-19 vaccines, observational data have been rapidly accumulating and thus far confirm that the benefits of vaccination outweigh the potential risks. This review examines the evidence supporting the effectiveness, immunogenicity, placental transfer, side effects, and perinatal outcomes of maternal covid-19 vaccination. Additionally, it describes factors associated with vaccine hesitancy in pregnancy. Overall, studies monitoring people who have received covid-19 vaccines during pregnancy have not identified any pregnancy specific safety concerns. Additional information on non-mRNA vaccines, vaccination early in pregnancy, and longer term outcomes in infants are needed. To collect this information, vaccination during pregnancy must be prioritized in vaccine research.

Introduction

On 11 March 2020, the World Health Organization declared the SARS-CoV-2 outbreak a worldwide pandemic.¹ To date, nearly 400 million cases of SARS-CoV-2 infection have been confirmed globally. Although stating the exact number of cases that have occurred in pregnant patients is difficult, recent statistics suggest that women of reproductive age make up more than 20% of the global population, and approximately 5% of women of reproductive age are pregnant at any given time.²⁻⁴ Therefore, several million cases of covid-19 during pregnancy are expected to have occurred in the past two years, making SARS-CoV-2 infection one of the most prevalent illnesses to affect this population.

Pregnant patients with symptomatic covid-19 infection are at increased risk for severe disease, with increased rates of hospital admission, intensive care unit (ICU) admission, intubation, and death.^{5,6} According to a recent systematic review, pregnant patients with covid-19 face higher rates of several adverse maternal outcomes as well as ICU admission (odds ratio 2.61, 95% confidence interval 1.84 to 3.71) and invasive ventilation (2.41, 2.13 to 2.7) compared with non-pregnant women of reproductive age with covid-19, and significantly higher rates of death (6.09, 1.82 to 20.38) compared with pregnant patients without covid-19.⁷ Given the risks faced by both pregnant patients and neonates,

understanding the immunologic response to vaccination in pregnancy is critically important. More than 100 vaccines were tested in clinical trials, with 12 vaccines currently in use.⁸ Given that pregnancy was an exclusion criterion in early clinical trials of vaccines, obstetric patients and their providers initially were required to make decisions about vaccination with limited data. To help to fill this gap, this review aims to summarize available data on the immunogenicity, effectiveness, adverse effects, and perinatal outcomes of maternal covid-19 vaccination, as well as on vaccine hesitancy during pregnancy. This review is aimed at clinicians caring for pregnant patients and researchers involved in vaccine development or public health.

Sources and selection criteria

We considered studies reporting on adult human populations who received covid-19 vaccination in pregnancy for inclusion in this review. An additional topic of interest was vaccine hesitancy in pregnancy. We did a comprehensive literature search to identify relevant articles. An experienced medical librarian developed and conducted search strategies, with input from the research team. We searched four bibliographic databases between November 2019 and March 2022: EBSCO's CINAHL (Cumulative Index of Nursing and Allied Health), Embase, MEDLINE via PubMed, and Web of Science Classic

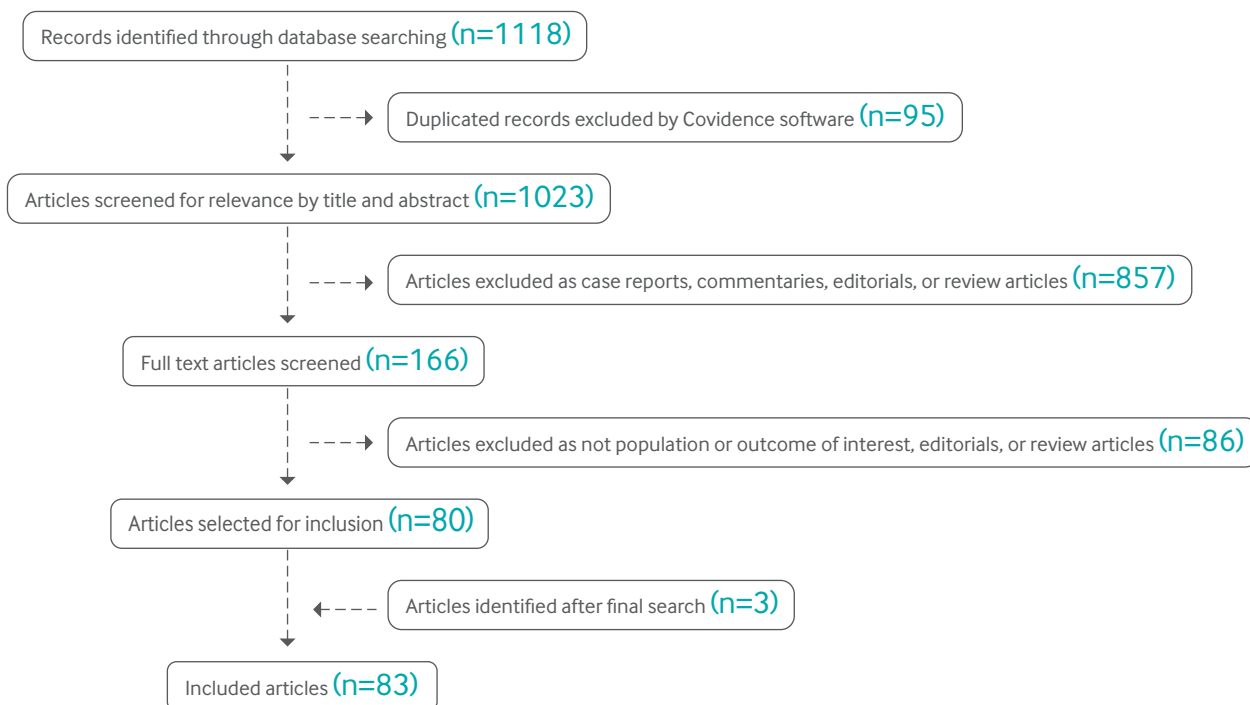


Fig 1 | Flow diagram of included articles

Core Collection (Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Sciences and Humanities, Book Citation Index- Science, Book Citation Index-Social Sciences and Humanities, Emerging Sources Citation Index, Current Chemical Reactions, Index Chemicus).

The searches combined controlled vocabulary supplemented with keywords related to the concepts of vaccination (for example, immunization, immunogenicity), pregnancy (for example, gestation, breastfeeding), covid-19 (for example, SARS-CoV-2, coronavirus), empirical methods (for example, prospective trial, cohort study), vaccine hesitancy (for example, uptake, unwillingness), and ethics related to vaccination during pregnancy (for example, therapeutic orphan, patient selection). We included articles written in the English language. We did not review preprints, and we did not include case reports. Searches were carried out on 8 February 2022 and rerun for updates on 8 March 2022 (fig 1).

We identified 45 studies evaluating the use of covid-19 vaccines in pregnancy via our search. Of these studies, 20 investigated immunogenicity, 10 investigated vaccine efficacy, 12 evaluated adverse effects of vaccines, and 26 evaluated perinatal outcomes after prenatal vaccination. We also included two additional studies published after our search given that their large sample size substantially expanded the available data on pregnancy outcomes after covid-19 vaccination. We also added one study on risk of congenital fetal anomalies after the search, as it specifically evaluated the association of covid-19 vaccination during the highest risk period

for teratogenicity. Of the 48 included studies, most reported the use of mRNA vaccines (43 included the Pfizer-BioNTech vaccine (BNT162b2); 28 included the Moderna vaccine (mRNA-1273)); only six reported use of the Johnson & Johnson-Janssen vaccine (Ad26.COV2.S), and five reported use of the Oxford-AstraZeneca vaccine (ChAdOx1-S). Some studies included multiple vaccine types, and some did not report the specific vaccine used. One study included two participants who received the Sinovac vaccine (CoronaVac; inactivated), three who received a combination of CoronaVac and Pfizer, and 78 who received Pfizer.⁹ The paper reported on infection rates during the era of the omicron variant, finding that fully vaccinated pregnant patients had milder illness, but did not break down the results by vaccine type. No other studies identified included inactivated vaccines. Vaccine hesitancy was evaluated in 42 studies. Several studies evaluated more than one outcome, so the total number of studies included in this review is 83.

Incidence/prevalence

Pregnancy is an independent risk factor for severe covid-19.⁵ Although the absolute risk for severe maternal morbidity and mortality is low, pregnancy remains a risk factor for hospital admission, ICU admission, and need for extracorporeal membrane oxygenation related to covid-19 compared with non-pregnant women.⁵ Covid-19 in pregnancy has also been associated with an increased risk of stillbirth and maternal death,^{7 10 11} and comorbidities such as advanced maternal age, obesity, diabetes, and heart disease further increase these risks. Moreover, several cases of intrauterine transmission of SARS-

CoV-2 have been carefully documented, although the risk seems to be low.¹² Additionally, neonates have been shown to be susceptible to severe illness from SARS-CoV-2 infection,¹³ so providing protection to the neonate through maternal vaccination is important. Neonates rely on the active placental transfer of maternal IgG for their protection against pathogens during the first six months of life,^{14 15} so vaccination during pregnancy has the potential to protect both mother and neonate.

Although vaccination with other respiratory viruses such as influenza during pregnancy has been shown to be highly successful and safe,¹⁶⁻¹⁸ these vaccinations have been the subject of ongoing research in the pregnant population for decades. Despite the clear harm SARS-CoV-2 infection poses to pregnant patients and their neonates, the paucity of initial safety and efficacy data on covid-19 vaccines in pregnancy led countries around the globe to take different positions on whether people should be vaccinated during pregnancy. According to the Covid-19 Maternal Immunization Tracker (COMIT), a website that provides global information on countries' public health policies regarding recommendations about covid-19 vaccines for pregnant and lactating people,¹⁹ 106 countries recommend covid-19 vaccination for some or all pregnant or lactating people, whereas 15 countries specifically recommend against vaccination in this population. Given the wide diversity of recommendations worldwide, the prevalence of people vaccinated for covid-19 during pregnancy likely also varies considerably. In the US, all major professional health organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM), have consistently recommended that everyone who is pregnant should be vaccinated against covid-19 since early 2021^{20 21}; however, as of April 2022, the US Vaccine Safety Datalink estimated that only 69.4% of pregnant women aged 18-49 years had been fully vaccinated with covid-19 vaccines before or during pregnancy.²²

Covid-19 vaccines

We identified four vaccines as having published data on their use in pregnancy: Pfizer-BioNTech, Moderna, Johnson & Johnson-Janssen, and Oxford-AstraZeneca (table 1). The Pfizer-BioNTech and Moderna mRNA vaccines had the most data in pregnancy. The mRNA vaccines work by releasing mRNA that encodes for the SARS-CoV-2 spike protein into cells, allowing the cell's machinery to produce the spike protein. Once mRNA from the vaccine has been read, it is destroyed. The body's immune cells then generate a response to the spike protein, creating the antibodies that provide immunity to SARS-CoV-2. The other two vaccines with data in pregnancy, the Oxford-AstraZeneca and Johnson & Johnson-Janssen vaccines, rely on an adenovirus vector to introduce DNA for the SARS-CoV-2 spike protein into the body's cells. The DNA is first copied into mRNA, and then, as with the mRNA vaccines, the

mRNA is used to produce copies of the spike protein, which then stimulate the immune system to create antibodies. Thus far, mRNA vaccines have shown better efficacy in the non-pregnant population than the viral vector vaccines for preventing symptomatic illness—with Pfizer and Moderna vaccines showing 95.0% and 94.1% efficacy, respectively, in the initial clinical trials—as well as severe disease, two weeks after the two dose series.^{23 25} By contrast, the Johnson & Johnson-Janssen vaccine was 72% effective in preventing symptomatic infection and 85% effective in preventing severe disease in the non-pregnant population,²⁷ and the AstraZeneca vaccine was 70.4% effective after two doses.²⁹ However, some of these differences between vaccines might be due to the variants circulating at the time of the trials.

As pregnancy was an exclusion criterion for these studies, which vaccine is the most effective in the pregnant population is unclear. More information on all vaccine types is needed, as many countries, including India, a country with approximately one sixth of the world's pregnant population, have no mRNA vaccines available. However, given the high morbidity from SARS-CoV-2 infection in pregnancy, most countries surveyed recommend covid-19 vaccination for some or all pregnant or lactating individuals.¹⁹ Most advocate for covid-19 vaccination regardless of previous infection and state that serologic testing, a pregnancy test, or a letter from an obstetric provider should not be required before vaccination. No recommendation for specific timing of vaccination in pregnancy exists; however, given that the primary goal of vaccination is to prevent maternal infection, most countries recommend vaccination regardless of pregnancy trimester. Pregnancy need not be delayed after covid-19 vaccination, as none of the currently available vaccines is a live vaccine.

Despite these strong recommendations for universal vaccination, vaccine hesitancy in the pregnant population remains high. Many people cite concern for fetal/infant wellbeing as a reason to decline vaccination, so more information on perinatal outcomes and transplacental antibody transfer is needed. Efforts are ongoing to fill these gaps, as a recent review of the clinicaltrials.gov website (accessed 23 March 2022) showed that 11 trials investigating covid-19 vaccinations in pregnancy are ongoing, including several prospective observational trials that are evaluating maternal and infant outcomes after covid-19 vaccination in pregnancy. These trials will hopefully provide additional information on the safety and efficacy of these vaccines and on the optimal timing and frequency of vaccination in pregnancy to maximize maternal and neonatal benefit.

Covid-19 vaccines in pregnancy

Vaccination during pregnancy can reduce disease related morbidity and mortality for pregnant people and their infants. Patients are at higher risk of significant morbidity from viral illnesses such as

Table 1 | Covid-19 vaccines with data in pregnancy

Vaccine	Manufacturer	Vaccine type	Dosing	Ages	Efficacy based on randomized clinical trials	Efficacy against severe covid-19	Current approval	Developmental and reproductive toxicity studies
BNT162b2	Pfizer-BioNTech ²³	mRNA: encodes stabilized spike, lipid nanoparticles	100 µg; 2 doses, 21 days apart	≥5 y	95.0% against symptomatic covid-19	88.9%	EUA: USA, UK, EU, Canada	Studies in rats showed no adverse effects on female mating performance, fertility, or any ovarian/uterine parameters or effects on embryo-fetal or postnatal survival, growth, or physical development ²⁴
mRNA-1273	Moderna ²⁵	mRNA: encodes stabilized spike, lipid nanoparticles	30 µg; 2 doses, 28 days apart	≥18 y	94.1% against symptomatic covid-19	100.0%	EUA: USA, UK, EU, Canada	DART studies in pregnant and lactating female rats did not show any adverse effects at clinically relevant 100 mg dose ²⁶
Ad26.CoV2.5	Johnson & Johnson-Janssen ²⁷	Recombinant replication incompetent human adenovirus vector encoding stabilized SARS-CoV-2 spike protein	5×10 ¹⁰ viral particles; 1 dose	≥18 y	66.1% against moderate to severe-critical covid-19	85.4%	EUA: USA, EU, Canada	No adverse effect on fertility, embryo-fetal, or postnatal development when twice human dose was injected in female rabbits 7 days before mating and at gestational days 6 and 20 (early and late gestation) ²⁸
ChAdOx1 (AZS1222)	Oxford-AstraZeneca ²⁹	Recombinant replication deficient chimpanzee adenoviral vector encoding SARS-CoV-2 spike protein	5×10 ¹⁰ viral particles; 2 doses, 4-12 weeks apart	≥18 y	70.4% against symptomatic covid-19	100.0%	EUA: WHO/Covax, UK, India, Mexico	DART studies have not shown harmful effects of vaccine in pregnant animals and their offspring ³⁰

DART=developmental and reproductive toxicity; EUA=emergency use authorization.

influenza if contracted during pregnancy,³¹ and other viral infections, such as Zika, rubella, and varicella, can cause serious neonatal morbidity if the primary infection occurs during pregnancy.³²⁻³⁴ Other viruses, such as pertussis, are relatively inconsequential for a pregnant person or a fetus, but pertussis infection in a young infant can be fatal. Immunizations have been shown to benefit all three populations—mother, fetus, and neonate—as any vaccine given to the mother can protect the neonate via the transplacental transport of IgG antibodies.¹⁴ However, although several vaccines are recommended in pregnancy, the optimal timing of the vaccination varies depending on the pathogen. Some vaccines, such as those for rubella and varicella, are recommended only during the preconception and postpartum period, as live vaccines theoretically could cause congenital infection if given during or just before pregnancy. By contrast, pertussis vaccination is recommended in every pregnancy, optimally between 27 and 36 weeks, to facilitate maximal placental antibody transfer for greatest protection of the neonate. Finally, influenza vaccines are recommended at any time in pregnancy during influenza season, as the priority is to prevent maternal infection. Current recommendations for covid-19 vaccines closely follow those for influenza vaccines—that is, the vaccine should be given as soon as possible in pregnancy for maternal benefit, given the significant increase in morbidity from SARS-CoV-2 infection seen in the pregnant population. Understanding how pregnancy affects response to covid-19 vaccination and subsequent placental antibody transfer is critical

to guiding vaccine recommendations for this special population.

Covid-19 vaccine immunogenicity data in pregnancy
Available data on the humoral and functional immune response to covid-19 vaccines in pregnancy are observational. Our review identified 20 studies evaluating the immunogenicity of covid-19 vaccines in pregnancy (table 2).³⁵⁻⁵⁴ Most studies evaluated immunogenicity of the Pfizer-BioNTech vaccine. A few studies did not clearly describe either the vaccine platform or the total number of participants; however, when described, this information is provided in table 2. Multiple studies support a robust maternal antibody response to covid-19 vaccination.^{40 42-45 51 54} A cohort study documented humoral immunity in pregnancy, with immunogenicity and reactogenicity similar to those observed in non-pregnant women; vaccine induced antibody titers were equivalent in pregnant and non-pregnant women.⁴² A few studies have found reduced immunogenicity in pregnancy compared with that observed in non-pregnant vaccinated women.^{38 35} One study found that pregnant women (n=390) had significantly lower serum SARS-CoV-2 IgG concentrations than non-pregnant women (n=260) (signal to cut-off ratio 27.03 v 34.35; P<0.001).³⁸ A smaller study observed a delay in the evolution of Fc receptor binding and functional antibody responses during pregnancy after initial vaccination; the response improved after the second dose but was still lower than in non-pregnant women.³⁵ An increase in maternal SARS-CoV-2 IgG antibody response with a

Table 2 | Immunogenicity data on covid-19 vaccines in pregnancy

Author; study design	Vaccine type	Total population	Gestational age at vaccination, weeks	Seropositive maternal blood	Seropositive cord blood
Alveo C, 2021 ³⁵ ; cohort study	Pfizer; 1st dose, n=32; 2nd dose, n=17. Moderna; 1st dose, n=32; 2nd dose, n=19	Pregnant: 1st dose, n=64; 2nd dose, n=36. Non-pregnant: 1st dose, n=13; 2nd dose, n=14	16.3-32.1 (range 16.3-32.1)	Fc receptor antibody concentrations were significantly lower in pregnancy v non-pregnant women after 1st dose. Fc receptor antibody concentrations increased significantly after 2nd dose but were still lower than in non-pregnant women	Vaccinated maternal/cord blood pairs (n=8): maternal titers of all antibodies higher than in cord blood; enriched RBD-specific FcγR3a binding in cord
Beharier O, 2021 ³⁶ ; multicenter cohort study	Pfizer	Vaccinated, n=86; infected, n=65; control, n=62	34.5 (SD 7.5)	Rise in anti-S and RBD IgG titers within 15 days of 1st dose. Additional risk in anti-S and RBD IgG after 2nd dose. Vaccinated: higher anti-S1 and RBD antibodies. Natural infection: higher anti-S2 and N antibodies	Cord blood IgG S1 and RBD did not differ between vaccinated and natural infection (P=0.70 and P=0.69, respectively). Higher transfer ratios in vaccinated for anti-S1, S2, and RBD IgG v natural infection (P<0.001)
Ben-Mayor B, 2022 ³⁷ ; prospective cohort study	Pfizer; 1st dose, n=19; 2nd dose, n=39	Vaccinated n=58	1st dose 34.5 ^{38,41} ; 2nd dose 37.1 ⁴¹⁻⁴³	Anti-S IgG >50 AU/mL detected in 53 samples	Anti-S IgG >50 AU/mL detected in 51 cord samples. Negative samples (n=7) all 1st dose to delivery interval of <27 days. SARS-CoV-2 IgG antibodies in maternal sera positively correlated with cord blood sera (ρ=0.857; R2 linear=0.719; P<0.001)
Bookstein P, 2021 ³⁸ ; observational case-control study	Pfizer; 2 doses	Pregnant, n=390; non-pregnant, n=260	Not reported	Pregnant women had significantly lower serum SARS-CoV-2 IgG concentrations than non-pregnant women (P<0.001). Pregnant (n=96): average serum IgG S1/CO ratio=27.03. Non-pregnant (n=96): average serum IgG S1/CO ratio=34.35	Not evaluated
Citu I, 2022 ³⁹ ; prospective cohort study	Pfizer; Janssen	Vaccinated, n=227; unvaccinated, n=608; covid-19 history, n=173; unvaccinated without covid-19 history, n=529; non-pregnant, n=227	Third trimester	Seronegative (n=173) v seropositive (n=54) pregnant patients: median anti-S IgG 0.41 (IQR 0.31-0.45) v 145 (98.2-208.1) U/mL (P<0.001) before vaccination; 1697 (393-2115) v 14571 (12628-15337) U/mL (P<0.001) at 2 months; 1083 (896-1468) v 10759 (9043-12571) U/mL (P<0.001) at 4 months. Pregnant (n=173) v non-pregnant (n=173) without history of SARS-CoV-2: anti-S IgG 0.41 (0.31-0.45) v 0.40 (0.32-0.47) U/mL (P=0.46) before vaccination; 1697 (1393-2115) v 1705 (1452-2179) U/mL (P=0.82) at 2 months; 1083 (896-1468) v 1114 (909-1482) U/mL (P=0.35) at 4 months	Not evaluated
Collier A, 2021 ⁴⁰ ; prospective cohort study	Pfizer, n=11; Moderna, n=19	Vaccinated, n=103; pregnant, n=30; non-pregnant, n=57. Infected, n=28; pregnant, n=22; non-pregnant, n=6	1st trimester, n=5; 2nd trimester, n=15; 3rd trimester, n=10	Pregnant vaccinated, median RBD IgG 27.601; non-pregnant vaccinated, median RBD IgG 37.839; pregnant infected, median RBD IgG 1321; pregnant vaccinated, median neutralizing titer 910; non-pregnant vaccinated, median neutralizing titer 901; pregnant infected, median neutralizing titer 148	Vaccinated: 9 paired maternal and infant cord blood samples. Median cord blood RBD IgG titers higher than maternal blood titers (19873 v 14953). Median cord neutralization IgG lower than maternal blood (324 vs 1016)
Gloekner S, 2022 ⁴¹ ; observational cohort study	Prime vaccine, AstraZeneca; boost vaccine 12 weeks later, Pfizer or Moderna	Pregnant, n=3; non-pregnant, n=25	Primary vaccine 21-28 weeks	Spike IgG detected in all samples. ID50 neutralization titers ≥160 in all maternal samples. Increase >1 log10 level after mRNA based boost	Spike IgG detected in all cord samples. ID50 neutralization titers ≥160 in all cord serum samples
Gray K, 2021 ⁴² ; prospective cohort study	Pfizer, n=41; Moderna, n=43. Non-pregnant: Pfizer, n=8; Moderna, n=8	Pregnant, n=84; non-pregnant, n=16	1st trimester, n=11; 2nd trimester, n=39; 3rd trimester, n=34	Robust, comparable IgG across pregnant and non-pregnant (pregnant, median 5.59 (IQR 4.68-5.89); non-pregnant, 5.62 (4.77-5.98); P=0.24). All titers significantly higher than pregnant with previous SARS-CoV-2 infection (P<0.001)	All 10 cord samples were positive for S and RBD IgG. Neutralizing antibody titers lower in umbilical cord than maternal sera; finding did not achieve statistical significance (maternal sera, median 104.7 (IQR 61.2-188.2); cord sera, 52.3 (11.7-69.6); P=0.05)
Kashani-Ligumsky L, 2021 ⁴³ ; cohort study	Pfizer, n=29	Infected, n=29; vaccinated, n=29; control, n=21	Not reported	Mean antibody titer 224.7 (SD 64.3) U/mL in vaccinated; 83.7 (91.6) U/mL in infected (P<0.05)	100% of infected and vaccinated cord blood samples anti-S IgG positive. Mean neonatal antibody titers higher in vaccinated (225 U/mL) v infected (83.7 U/mL) (P<0.05)
Kugelmann N, 2021 ⁴⁴ ; prospective cohort study	Pfizer, n=130	Vaccinated, n=130	24.9 (SD 3.3)	100% positive for SARS-CoV-2 IgG. Change in maternal antibody level per 1 week increase from 2nd vaccine dose to birth: -10.9% (95% CI -17.2% to -4.2%; P=0.002). Change in maternal antibody level per 1 year increase in maternal age: -5.3% to -0.9%; P=0.007	100% positive for SARS-CoV-2 IgG; IgG titers 2.6x higher than maternal titers. Change in newborn antibody level per 1 week increase from 2nd vaccine dose to birth: -11.7% (95% CI -19.0% to -3.8%; P=0.005). Change in newborn antibody level per 1 year increase in maternal age: -2.7% (-5.2% to -0.1%, P=0.04)

(Continued)

Table 2 | Continued

Author; study design	Vaccine type	Total population	Gestational age at vaccination, weeks	Seropositive maternal blood	Seropositive cord blood
Mithal L, 2021 ⁴⁵ ; prospective case series	Pfizer, n=18; Moderna, n=6; unknown, n=4	Vaccinated, n=27	33 (SD 2)	SARS-CoV-2 IgG: 26/27 (97%)	SARS-CoV-2 IgG: 25/28 (89%). Negative cases had 1st dose <3 weeks before delivery. IgG transfer ratio 1.0 (SD 0.6). Increased latency from vaccination to delivery associated with increased transfer ratio ($\beta=0.2$, 95% CI 0.1 to 0.2). Second dose before delivery was associated with increased infant IgG levels ($\beta=19.0$, 7.1 to 30.8). Latency from vaccination to delivery was associated with increased infant IgG levels ($\beta=2.9$, 0.7 to 5.1)
Nir O, 2021 ⁴⁶ ; prospective cohort study	Pfizer	Fully vaccinated, n=64; unvaccinated and recovered from covid-19, n=11	33.5 (SD 3.2)	100% positive for SARS-CoV-2 IgG. SARS-CoV-2 IgG: 26.1 (IQR 22.0-39.7) in vaccinated v 2.6 (0.9-3.5) in recovered (P<0.001)	98.3% positive for SARS-CoV-2 IgG. SARS-CoV-2 IgG: 20.2 (12.7-29.0) in vaccinated v 3.27 (0.5-4.6) in recovered (P<0.001)
Prabhu M, 2021 ⁴⁷ ; cohort study	Pfizer, n=85; Moderna, n=37	One dose, n=55; two doses, n=67	Not reported	SARS-CoV-2 IgG: 43.6% after 1 dose; 98.5% after 2 doses. Maternal IgG levels were significantly higher, week by week, starting 2 weeks after first vaccine dose (P=0.005 and 0.019, respectively)	SARS-CoV-2 IgG: 44% after 1 dose; 99% after 2 doses. Placental transfer ratio correlated with number of weeks elapsed since maternal vaccine dose 2 (R=0.8; P=2.6e-15). All but one cord blood samples had detectable IgG antibodies by 4 weeks after vaccine dose 1. One dyad with no transfer of antibodies to neonate was 10 weeks from dose 1 and 6 weeks from dose 2
Rottenreich A, 2021 ⁴⁸ ; prospective cohort study	Pfizer, n=20	Fully vaccinated, n=20	All 3rd trimester	SARS-CoV-2 anti-S and anti-RBD: 100%	SARS-CoV-2 anti-S and anti-RBD: 100%; placental transfer ratios 0.44 (IQR 0.25-0.61) for anti-S IgG and 0.34 (0.27-0.56) for anti-RBD IgG. SARS-CoV-2 anti-S and anti-RBD specific IgG levels in maternal sera were positively correlated with respective cord blood (p s=0.72; P<0.001 and p s=0.72; P<0.001, respectively). Cord blood titers directly correlated with increasing time from 1st vaccine dose (ps=0.71; P=0.001 and ps=0.63; P=0.004, respectively)
Rottenreich A, 2022 ⁴⁹ ; cohort study	Pfizer, n=171	First dose at 27-31 weeks, "early 3rd trimester," (n=83); first dose at 32-36 weeks, "late 3rd trimester," (n=88)	All 3rd trimester	100% SARS-CoV-2 anti-S and anti-RBD. Median anti-S specific and anti-RBD specific IgG at time of delivery were lower in those vaccinated in early 3rd trimester v late 3rd trimester	100% SARS-CoV-2 anti-S and anti-RBD. Anti-RBD specific IgG concentrations in neonatal sera were higher after early v late 3rd trimester vaccination (median 9620 (IQR 5131-15332) AU/mL v 6697 (3157-14731) AU/mL; P 0.02). Median antibody placental transfer ratios were increased after early v late 3rd trimester immunization (anti-S ratio 1.3 (IQR 1.1-1.6) v 0.9 (0.6-1.1); anti-RBD specific ratio 2.3 (1.7-3.0) v 0.7 (0.5-1.2); P<0.001). Neutralizing antibodies placental transfer ratio was greater after early v late third trimester immunization (median 1.9 (1.7-2.5) v 0.8 (0.5-1.1); P<0.001). Neutralizing antibodies placental transfer ratio positively associated with longer duration from vaccination (r=0.77; P<0.001)
Rottenreich M, 2022 ⁵⁰ ; prospective cohort study	Pfizer	Vaccinated, n=402	1st trimester, n=90; 2nd trimester, n=124; 3rd trimester, n=188	1st trimester: anti-S IgG 76 AU/mL; anti-RBG IgG 4.78 AU/mL. 2nd trimester: anti-S IgG 126 AU/mL; anti-RBG IgG 1263 AU/mL. 3rd trimester: anti-S IgG 240 AU/mL; anti-RBG IgG 5855 AU/mL. Vaccine in 1st trimester with booster dose in 3rd trimester: anti-S IgG 1665 AU/mL; anti-RBG IgG:20946 AU/mL	All 402 neonates positive for anti-S and anti-RBG IgG. 1st trimester: anti-S IgG 126 AU/mL; anti-RBG IgG 1140 AU/mL. 2nd trimester: anti-S IgG 204 AU/mL; anti-RBG IgG 8038 AU/mL. 3rd trimester: anti-S IgG 255 AU/mL; anti-RBG IgG 8038 AU/mL. 3rd trimester, 27-31 weeks: anti-RBG IgG 6811 AU/mL; transfer ratio 2.4. 3rd trimester, 32-36 weeks: anti-RBG IgG 9516 AU/mL; transfer ratio 0.8 (P<0.0001). Vaccine in 1st trimester with booster dose in 3rd trimester: anti-S IgG 528 AU/mL; anti-RBG IgG 4225 AU/mL
Shames E, 2021 ⁵¹ ; cohort study	Pfizer, n=49; Moderna, n=25; mRNA unknown type, n=9	Vaccinated, n=84; unvaccinated, n=116	All 3rd trimester	Vaccinated, n=52: anti-SARS-CoV-2 IgG 22.8 (SD 14.5). Unvaccinated, n=116: anti-SARS-CoV-2 IgG 0.04 (0.05). P<0.001	Not evaluated

(Continued)

Table 2 | Continued

Author; study design	Vaccine type	Total population	Gestational age at vaccination, weeks	Seropositive maternal blood	Seropositive cord blood
Shen C, 2022 ⁵² ; prospective cohort study	Moderna, n=29	Vaccinated: 1 dose, n=4; 2 doses, n=25	1st dose, 28.45 (SD 2.64); 2nd dose, 33.31 (2.13)	Wild type variant: SARS-CoV-2 neutralizing IgG 40.32% after 1 dose; 97.46% after 2 doses. Delta variant: SARS-CoV-2 neutralizing IgG 4.01% after 1 dose; 80.49% after 2 doses	Wild type variant: SARS-CoV-2 neutralizing IgG 43.33% after 1 dose; 97.37% after 2 doses. Delta variant: SARS-CoV-2 neutralizing IgG 1.44% after 1 dose; 66.25% after 2 doses. Wildtype variant: cord to maternal ratio 1.07 after 1 dose; 0.99 after 2 doses. Delta variant: cord to maternal ratio 0.92 after 1 dose; 0.90 after 2 doses
Trostle M, 2021 ⁵³ ; prospective cohort study	Pfizer, n=26; Moderna, n=10	Vaccinated, n=36	1st trimester, n=2; 2nd trimester, n=30; 3rd trimester, n=4	Not evaluated	100% SARS-CoV-2 anti-S; 34 titers >250U/mL; 2 with titers <250 U/mL were both vaccinated >20 weeks before delivery
Yang YJ, 2021 ⁵⁴ ; retrospective cohort study	Pfizer, n=1025; Moderna, n=301; Janssen, n=33	Vaccinated, n=1359	First dose: pre-pregnancy, n=38; 1st trimester, n=193; 2nd trimester, n=699; 3rd trimester, n=429	Anti S IgG in all women—pre-pregnancy: Pfizer 3.7, Moderna 4.8, Janssen NA; 1st trimester: Pfizer 3.9, Moderna 4.8, Janssen 3.6; 2nd trimester: Pfizer 4.8, Moderna 5.7, Janssen 3.0; 3rd trimester: Pfizer 6.2, Moderna 6.6, Janssen 2.5. Anti-S IgG in fully vaccinated women (≥14 days after final dose)—pre-pregnancy: Pfizer 3.7, Moderna 4.8, Janssen NA; 1st trimester: Pfizer 3.9, Moderna 4.8, Janssen 3.6; 2nd trimester: Pfizer 4.8, Moderna 5.7, Janssen 3.0; 3rd trimester: Pfizer 6.4, Moderna 7.1, Janssen 2.5	Cord blood anti-S IgG (maternal titers) in those with no history of infection: pre-pregnancy 4.5 (SD 4.1); 1st trimester 4.7 (4.2); 2nd trimester 5.5 (4.9); 3rd trimester (1 dose) 2.5 (3.4); 3rd trimester (2 doses) 4.1 (5.3); 3rd trimester (fully vaccinated) 6.3 (6.2). Booster received in 3rd trimester (no infection): pregnancy 8.1 (8.3); 1st trimester 7.1 (8.3). History of infection: pre-pregnancy 8.5 (8.9); 1st trimester 6.7 (6.4); 2nd trimester 6.9 (6.4); 3rd trimester (1 dose) 5.7 (6.4); 3rd trimester (2 doses) 6.9 (7.5); 3rd trimester (fully vaccinated) 7.4 (7.4)

CI=confidence interval; IQR=interquartile range; N=nucleocapsid; NA=not applicable; RBD=receptor binding domain; S=spike; S/CO=signal to cut-off ratio; SD=standard deviation.

second dose in pregnancy was also documented by a study that found significantly higher maternal IgG concentrations, week by week, starting two weeks after the first vaccine dose, as well as between the first and second weeks after the second vaccine dose ($P<0.005$ and $P=0.019$, respectively).⁴⁷ Another study also found higher antibody concentrations during pregnancy after two doses compared with one dose of Moderna vaccine.⁵²

Two studies evaluated the maternal immunogenicity after a third trimester booster vaccination.^{49 54} A prospective cohort study found considerable antibody waning throughout pregnancy in those vaccinated in the first trimester, with a boosting effect of a third vaccine dose.⁴⁹ Booster dose administration was associated with significantly increased maternal and neonatal antibody concentrations compared with those who completed the two dose vaccine series in the first trimester without a booster dose ($P<0.001$). In a retrospective study of 1359 pregnant women, completion of the vaccination course, history of SARS-CoV-2 infection, and a third trimester booster dose were associated with the highest maternal and umbilical cord antibody concentrations.⁵⁴ These immunogenicity studies highlight the importance of adherence to full vaccination recommendations in pregnancy and additionally support the benefit of a booster dose in pregnancy to optimize immunity.

Several studies documented a more robust maternal antibody response to vaccination than to previous infection.^{36 39 40 42 43 46} One found significantly higher SARS-CoV-2 IgG concentrations in maternal serum and cord blood among fully vaccinated women ($n=64$) ($P<0.001$) compared with 11 previously infected pregnant women.⁴⁶ Vaccination during pregnancy may also provide protection for the newborn. We identified 16 studies that documented presence of SARS-CoV-2 antibodies in cord blood after maternal vaccination.^{35 36 40-49 51-53} Additionally, several studies have shown a positive correlation between maternal serum and cord blood antibody concentrations, which is generally described as the placental transfer ratio.^{36 40 45 46 48 49 52} With regard to timing of antibody production, one study found maternal antibody production as early as five days after a first vaccine dose and transplacental transfer as early as 16 days after a first dose.⁴⁷ Some variability exists, however, and lack of transfer was seen in one neonate who was delivered six weeks after the second dose. Another study found that the three of 28 cord samples that were IgG negative all came from deliveries with less than three weeks between the time of first dose and delivery.⁴⁵ Maternal IgG concentrations and placental IgG transfer ratios increased over time, suggesting that time between vaccination and birth may be an important factor.

The degree of maternal protection via placental transfer of antibodies likely depends on maternal antibody concentration, which is related to timing of vaccination and delivery. In one study, early third trimester (27-31 weeks) vaccination was associated

with higher neonatal anti-SARS-CoV-2 antibody and serum neutralizing activity. This may support early third trimester as the optimal timing for a booster vaccination to optimize maternal to fetal antibody transfer for neonatal protection.⁴⁹ In general, transplacental antibody transfer starts in the second trimester; however, transfer is most efficient in the third trimester.^{55 56}

More studies of factors affecting placental antibody transfer are needed, along with better understanding of the degree of protection provided. Although we identified 20 studies evaluating the immunogenicity of covid-19 vaccines in pregnancy, they were primarily on mRNA vaccines. These limited data highlight the importance of fully understanding the immunology of pregnancy to develop evidence based, pregnancy specific vaccine recommendations. Overall, the immunogenicity data in pregnancy illustrate a robust immune response to vaccination and maternal transfer of antibodies to the neonate via cord blood.

Covid-19 vaccines in prevention of maternal and infant infection

We identified nine articles evaluating risk of maternal SARS-CoV-2 infection after maternal vaccination.^{9 57-64} The data overwhelming support maternal vaccination as being effective at reducing the risk for infection and severe illness. A large national prospective cohort study in Scotland of 18399 vaccinated and 126149 unvaccinated pregnant women found that 77.4% (3833/4950; 95% confidence interval 76.2% to 78.6%) of SARS-CoV-2 infections, 90.9% (748/823; 88.7% to 92.7%) of SARS-CoV-2 associated hospital admissions, and 98% (102/104; 92.5% to 99.7%) of SARS-CoV-2 associated critical care admission occurred in those who were unvaccinated.⁶³ In Israel, a large observational cohort of 10861 vaccinated pregnant women matched to 10861 unvaccinated pregnant controls found an estimated vaccine effectiveness from seven through 56 days after the second dose of 96% (95% confidence interval 89% to 100%) for any documented infection, 97% (91% to 100%) for infections with documented symptoms, and 89% (43% to 100%) for covid-19 related hospital admission.⁶⁰

These results reflect effectiveness mainly against the original SARS-CoV-2 reference strain and the B.1.1.7 (alpha) variant, as these were the dominant strains circulating during the study period. This is similar to the vaccine effectiveness estimated in the general population in Israel. A retrospective cohort study in the US of 1332 vaccinated pregnant patients and 8760 incompletely vaccinated or unvaccinated pregnant patients found that vaccinated patients had lower odds of severe covid-19, defined as SpO₂ <94% on room air, PaO₂/FiO₂ ratio <300 mm Hg, respiratory rate >30 breaths per minute, or lung infiltrates >50%, or critical covid-19, defined as respiratory failure, septic shock, or multiple organ failure (0.08% v 0.66%; adjusted odds ratio 0.10, 95% confidence

interval 0.01 to 0.49) and covid-19 of any severity (1.1% v 3.3%; 0.31, 0.17 to 0.51).⁶² These and the other smaller studies show an association between maternal SARS-CoV-2 vaccination and lower odds of covid-19 illness. Overall, covid-19 vaccines have been found to be highly effective in preventing severe illness, hospital admission, and death; these data support similar effectiveness in pregnancy.

Additionally, one study evaluated the effectiveness of maternal vaccination during pregnancy against covid-19 related hospital admission in infants during the first six months of life.⁶⁵ Of 176 infants admitted with covid-19, 16% of their mothers had been vaccinated compared with 32% of 203 infants admitted without covid-19 (P<0.01). Effectiveness of maternal vaccination during pregnancy against covid-19 related hospital admission in infants aged <6 months was found to be 61% (31% to 78%). Effectiveness of a two dose covid-19 vaccination series was 32% (-43% to 68%) in the first 20 weeks of pregnancy and 80% (55% to 91%) after 21 weeks through 14 days before delivery. This gestational age breakdown has wide confidence intervals and should be interpreted with caution. Overall, completion of a two dose mRNA covid-19 vaccination series during pregnancy seems to reduce covid-19 related hospital admissions among infants aged <6 months, but the duration of clinical protection remains uncertain. A smaller study evaluating antibody response in infants found that most infants (98%; 48/49) had detectable anti-S IgG antibodies at 2 months of life after maternal vaccination and 57% (16/28) still had detectable concentrations at 6 months.⁶⁶ This was compared with only 8% (1/12) with detectable antibodies after SARS-CoV-2 infection during pregnancy. The concentrations of antibodies needed to provide protection in infants is unknown, so clinical data in correlation with titer information are needed. However, given the burden of SARS-CoV-2 in infants and that covid-19 vaccines are not planned for infants <6 months, these findings provide support that babies receive protective benefits from maternal vaccination.

COVID-19 vaccines and perinatal outcomes

On the basis of 26 studies describing perinatal outcomes after covid-19 vaccination in pregnancy, the overall rates of adverse perinatal outcomes were not increased after maternal vaccination (table 3). The rates of preterm birth, fetal growth restriction, cesarean delivery, and neonatal intensive care unit (NICU) admission varied across studies, which is likely explained by different patient populations; however, in the studies with a comparison group of unvaccinated pregnant patients, the rates were not significantly increased. Some challenges in evaluating perinatal outcomes after exposure during pregnancy include understanding the baseline risk of the outcome, the timing of the exposure in pregnancy related to the outcome, and the necessary sample size needed to detect a difference. Additionally, common sources of bias in maternal vaccination

Table 3 | Perinatal outcome data with covid-19 vaccines in pregnancy

Author; country; study design	Vaccine type	Population with delivery outcomes	Perinatal outcomes
Kharbanda E, 2021 ⁶⁷ ; USA; case-control surveillance study	Pfizer, n=8267; Moderna, n=6313; Janssen, n=528	Pregnant vaccinated, n=15 108; pregnant unvaccinated, n=90 338	SAB: 1128/13 160 (8.6%) SAB occurred within 28 days of vaccination; 20 139/250 994 (8.0%) of ongoing pregnancies occurred within 28 days of vaccination. Among women with SAB, odds of covid-19 vaccine exposure were not increased in previous 28 days compared with women with ongoing pregnancies (AOR 1.02, 95% CI 0.96 to 10.8)
Zauche L, 2021 ⁶⁸ ; USA; cohort study	Pfizer, n=1294; Moderna, n=1162	Vaccinated, n=2456	Cumulative SAB risk from 6 to <20 weeks was 14.1% (95% CI 12.1% to 16.1%). With direct maternal age standardization, SAB risk was 12.8% (10.8% to 14.8%). Cumulative risk of SAB increased with maternal age. Compared with data from two historical cohorts that represent lower and upper ranges of SAB risk, cumulative risks of spontaneous abortion were within expected risk range
Magnus M, 2021 ⁶⁹ ; Norway; case-control study	Pfizer, n=790; Moderna, n=137; AstraZeneca, n=76	Vaccinated, n=958; unvaccinated, n=13 613	SAB: AOR for vaccinated/unvaccinated 0.81 (95% CI 0.69 to 0.95) for vaccination in the previous 5 weeks
Trostle M, 2021 ⁷⁰ ; USA, case series	Pfizer, n=332; Moderna, n=92	Vaccinated, n=424; delivered liveborn infant, n=85	SAB 6.5%; preterm birth 5.9%; FGR/SGA 12.2%; cesarean delivery 35.3%; fetal anomaly 1.2%; stillbirth 0%; NICU admission 15.3%; any antenatal complication 23.5%
Rottensteich M, 2022 ⁵⁰ ; Israel; Multicenter retrospective database study	Pfizer, n=712	Two doses, n=712; unvaccinated, n=1063	Preterm birth: vaccinated 1%; unvaccinated 0.9% (P=0.93). FGR/SGA: vaccinated 11.4%; unvaccinated 9.2% (P=0.14). Cesarean delivery: vaccinated 15.6%; unvaccinated 10.8% (P<0.01). Stillbirth: vaccinated 0.7%; unvaccinated 0.5% (P=0.52). NICU admission: vaccinated 4.1%; unvaccinated 4.5% (P=0.65). Composite adverse maternal outcome: vaccinated 24.2%; unvaccinated 23.6% (AOR 0.8, 95% CI 0.61 to 1.03; P=0.79). Composite adverse neonatal outcome: vaccinated 7.9%; unvaccinated 11.4% (AOR 0.5, 0.36 to 0.74; P=0.02)
Shimabukuro T, 2021 ⁷¹ ; USA; V-safe Surveillance System and VAERS Pregnancy Registry	Pfizer: 1 dose, n=9052; 2 doses, n=6638. Moderna: 1 dose, n=7930; 2 doses, n=5635	n=827 with completed pregnancy outcome	Preterm birth 9.4%; FGR/SGA 3.2%; major congenital anomaly 2.2%; SAB 12.6%; stillbirth 0.1%; neonatal death 0%
Theiler R, 2021 ⁶⁴ ; USA; cohort study	Pfizer, n=127; Moderna, n=12; Janssen, n=1	Vaccinated, n=140; unvaccinated, n=1862	Preterm birth: vaccinated 9.3%; unvaccinated 8.5% (P=0.70). FGR/SGA: vaccinated 7.9%; unvaccinated 6.5% (P=0.53). Cesarean delivery: vaccinated 31.4%; unvaccinated 29.8% (P=0.65). Stillbirth: vaccinated 0%; unvaccinated 0.3% (P=1.0). NICU admission: vaccinated 0.07%; unvaccinated 0.6% (P=0.58) (for >1day, >37weeks, >2500 g). Any antenatal complication: vaccinated 5%; unvaccinated 4.9% (P=0.95)
Dick A, 2022 ⁷² ; Israel; retrospective cohort study	Pfizer or Moderna	Vaccinated, n=2305; unvaccinated, n=3313	Preterm birth: vaccinated 5.5%; unvaccinated 6.2% (P=0.31). Only significant finding: 2nd trimester vaccination had increased risk of preterm birth compared with unvaccinated counterparts (8.1% v 6.2%; P<0.001). FGR/SGA: vaccinated 6.2%; unvaccinated 7.0% (P=0.2). Cesarean delivery: vaccinated 15.5%; unvaccinated 16.0%. Stillbirth: vaccinated 0.87%; unvaccinated 1.0%
Lipkind H, 2022 ⁷³ ; USA; observational retrospective cohort study	Pfizer, n=5478; Moderna, n=4162; Janssen, n=424	Vaccinated, n=10 064; unvaccinated n=36 015	Preterm birth: vaccinated 4.9%; unvaccinated 7.0% (AHR 0.91, 95% CI 0.82 to 1.01; P=0.06). FGR/SGA: vaccinated 8.2%; unvaccinated 8.2% (AHR 0.95, 0.87 to 1.03; P=0.24)
Goldstein I, 2022 ⁶¹ ; Israel; cohort study	Pfizer	Infants of unvaccinated mothers, n=7591; infants of vaccinated mothers, n=16 697	Preterm birth: vaccinated 4.4%; unvaccinated 4.1% (RR 0.95, 95% CI 0.83 to 1.10). FGR/SGA: vaccinated 6.6%; unvaccinated 6.7% (RR 0.97, 0.87 to 1.08). Fetal anomaly: first trimester vaccination—unvaccinated, n=3584; vaccinated, n=213; risk of any congenital malformations—RR 0.69, 0.44 to 1.04; risk for major heart malformations was lower among exposed group (RR 0.46, 0.24 to 0.82)
Citu I, 2022 ³⁹ ; Romania; prospective cohort study	Pfizer; Janssen	Vaccinated, n=173; unvaccinated, n=529	Preterm birth: vaccinated 8.1%; unvaccinated 6.9% (P=0.63). FGR/SGA: vaccinated 3.4%; unvaccinated 4.9% (P=0.43). Cesarean delivery: vaccinated 11.5%; unvaccinated 13.0% (P=0.61)
Bookstein P, 2021 ³⁸ ; Israel; observational case-control study	Pfizer	Vaccinated, n=57	Preterm birth 0%; FGR/SGA 5.3%; cesarean delivery 17.6%; stillbirth/neonatal death 0%; NICU admission 3.5%; hypertensive disorder of pregnancy 1.8%
Beharier O, 2021 ³⁶ ; Israel; multicenter cohort study	Pfizer	Vaccinated, n=92; infected, n=74; control, n=66; delivery outcomes, n=92	Preterm birth: vaccinated 7.6%; infected 10.5%; control 4.3% (NS). NICU admission: vaccinated 4.3%; infected 2.7%; control 1.6% (NS)
Magnus M, 2022 ⁷⁴ ; Norway, Sweden; registry based retrospective cohort study	Pfizer, n=20 424; Moderna, n=7607; AstraZeneca, n=475	Vaccinated, n=28 506; unvaccinated, n=129 015	Preterm birth: vaccinated 6.2 v unvaccinated 4.9 per 10 000 pregnancy days at risk (AHR 0.98, 95% CI 0.91 to 1.05). Similar for 2nd and 3rd trimester vaccination, with 1 or 2 doses, and for both mRNA vaccines. SGA: vaccinated 7.8%; unvaccinated 8.5% (AOR 0.97, 0.90 to 1.04). Stillbirth: vaccinated 2.1 v unvaccinated 2.4 per 100 000 pregnancy days at risk (AHR 0.86, 0.63 to 1.17). NICU admission: vaccinated 8.5% v unvaccinated 8.5% (AOR 0.97, 0.86 to 1.10)
Gray K, 2021 ⁴² ; prospective cohort study	Pfizer, n=41; Moderna, n=43	Vaccinated, n=13	Preterm birth 8%; FGR 0%; cesarean delivery 23%; NICU admission 15%
Morgan J, 2022 ⁶² ; USA; retrospective cohort study	Pfizer, n=883; Moderna, n=382; Janssen, n=67	Vaccinated, n=1332; incompletely vaccinated or unvaccinated, n=8760	Stillbirth: vaccinated 0%; unvaccinated 0.07% (OR 0, 95% CI 0 to 4.73). Maternal death: vaccinated 0%; unvaccinated 0.01% (OR 0, 0 to 651)

(Continued)

Table 3 | Continued

Author; country; study design	Vaccine type	Population with delivery outcomes	Perinatal outcomes
Aslam J, 2022 ⁷⁵ ; Pakistan; Observational study	Not described	Pregnant in high dependency unit and ICU, n=33; vaccinated, n=6; unvaccinated, n=27	Stillbirth: n=16, all unvaccinated. Neonatal death: n=3, all unvaccinated. Maternal death: n=22, all unvaccinated
Wainstock T, 2021 ⁷⁶ ; Israel; Retrospective cohort study	Pfizer, n=913	Vaccinated, n=913; unvaccinated, n=3486	FGR/SGA: vaccinated 2.8%; unvaccinated 3.8% (OR 0.75, 95% CI 0.49 to 1.15). Cesarean delivery: vaccinated 19.9%; unvaccinated 17.2% (OR 1.19, 0.99 to 1.44)
Blakeway H, 2022 ⁵⁷ ; UK; retrospective cohort study	Pfizer, n=109; Moderna, n=18; AstraZeneca, n=13	Vaccinated, n=133; unvaccinated, n=399	FGR/SGA: vaccinated 12%; unvaccinated 12% (P>1.0). Cesarean delivery: vaccinated 30.8%; unvaccinated 34.1% (P=0.49). Stillbirth: vaccinated 0%; unvaccinated 0.2% (P=NE). NICU admission: vaccinated: 5.3%; unvaccinated 5.0% (P=0.93). Fetal abnormality: vaccinated 2.2%; unvaccinated 2.5% (P=0.87)
Bleicher I, 2021 ⁵⁸ ; Israel; prospective cohort study—interim analysis of broader observations study—questionnaire	Pfizer, n=202	Vaccinated, n=202; unvaccinated, n=124	FGR/SGA: vaccinated 1.5%; unvaccinated 0% (P=0.29). Fetal anomaly: vaccinated 4.5%; unvaccinated 4.8% (P=1.0). Composite pregnancy complications: vaccinated 16%; unvaccinated 20% (P=0.37)
Ruderman R, 2022 ⁷⁷ ; USA; cohort study	Not described	Vaccinated within teratogenic window, n=1149; vaccinated outside teratogenic window, n=1473; unvaccinated, n=534	Congenital anomalies: vaccinated within teratogenic window—30 days before conception to 14 weeks 48/1149 (4.2%); 2-10 weeks 34/840 (4.0%); vaccinated outside teratogenic window—30 days before conception to 14 weeks 61/1473 (4.1%); 2-10 weeks 75/1782 (4.2%); unvaccinated or vaccinated outside teratogenic window—30 days before conception to 14 weeks 88/2007 (4.4%); 2-10 weeks 102/2316 (4.4%); odds ratios between unvaccinated or vaccinated outside teratogenic window and vaccinated within teratogenic window non-significant; odds ratios between vaccinated outside teratogenic window and vaccinated within teratogenic window non-significant
Fell D, 2022 ⁷⁸ ; Canada; retrospective cohort study	Pfizer, n=18 101; Moderna, n=4507; other, n=52	Vaccinated, n=22 660; vaccinated after pregnancy, n=44 815; unvaccinated, n=30 115	Cesarean delivery: vaccinated 30.8%; vaccinated after pregnancy 32.2% (ARR 0.92, 95% CI 0.89 to 0.95); unvaccinated 28.5%. NICU admission: vaccinated 11.0%; vaccinated after pregnancy 13.3% (ARR 0.85, 0.80 to 0.90); unvaccinated 12.8% (ARR 0.92, 0.87 to 0.97)
Nir O, 2021 ⁴⁶ ; Israel; prospective cohort study	Pfizer	Fully vaccinated, n=64; unvaccinated and recovered from covid-19, n=11	Cesarean delivery: vaccinated 36%; recovered 27.3%
Rottensteich A, 2022 ⁴⁹ ; Israel; cohort study	Pfizer	First dose at 27-31 weeks, "early 3rd trimester," n=83; first dose at 32-36 weeks, "late 3rd trimester," n=88	Cesarean delivery: vaccinated early 3rd trimester 7.2%; late 3rd trimester 8.0%
Kashani-Ligumsky L, 2021 ⁴³ ; Israel; cohort study	Pfizer	Infected, n=29; vaccinated, n=29; control, n=21	Vaginal delivery: vaccinated 89.7%; infected 82.8%; control 85.7% (P=0.86)
Shanes F, 2021 ⁵¹ ; USA; cohort study	Pfizer, n=49; Moderna, n=25; mRNA unknown type, n=9	Vaccinated, n=84; unvaccinated, n=116	Vaginal delivery: vaccinated 79%; unvaccinated 65% (P=0.04). No difference in decidual arteriopathy, fetal vascular malperfusion, or low or high grade chronic villitis

AHR=adjusted hazard ratio; AOR=adjusted odds ratio; ARR, adjusted risk ratio; CI, confidence interval; FGR=fetal growth restriction; HR=hazard ratio; NE=not estimatable; NICU=neonatal intensive care unit; NS=not significant; OR=odds ratio; SAB=spontaneous abortion; SGA=small for gestational age; RR=risk ratio.

observational studies including healthy vaccinee bias and confounding by indication, immortal time bias, and cohort truncation must be considered.⁷⁹

A large registry based study of births in Sweden and Norway (28 506 vaccinated; 129 015 unvaccinated) found no significant increased risk of adverse pregnancy outcomes including preterm birth, stillbirth, small for gestational age, or NICU admission in people vaccinated against SARS-CoV-2 during pregnancy.⁷⁴ The results were similar for vaccinations during the second or third trimester, with one or two doses of vaccine, and with different mRNA vaccine types. A large (>10 000 people vaccinated during pregnancy) US based multisite retrospective cohort with a diverse population and comprehensive data on vaccination did not find an increase in preterm birth or small for gestational age birth.⁷³ Additionally, a large (913 vaccinated; 3486 unvaccinated) retrospective cohort in Israel found no differences in pregnancy, delivery, or newborn complications, including gestational age at delivery, incidence of small for gestational age birth, and newborn respiratory complications.⁷⁶

Another important perinatal outcome of interest after maternal vaccination is risk of spontaneous abortion. Studies evaluating this risk should ideally include a control group and document timing of maternal vaccination. We identified four studies on risk of spontaneous abortion after covid-19 vaccinations in pregnancy.⁶⁷⁻⁷⁰ One used the Vaccine Safety Datalink to analyze the odds of receiving a covid-19 vaccine in the 28 days before a spontaneous abortion.⁶⁷ It found that pregnancies ending in a spontaneous abortion did not have an increased odds of exposure to a covid-19 vaccination in the previous 28 days compared with ongoing pregnancies (adjusted odds ratio 1.02, 0.96 to 1.08). Results were consistent for Moderna and Pfizer vaccines and by gestational age group. Additionally, a case-control study from Norwegian registries of 13 956 women with ongoing pregnancies (958 vaccinated) found adjusted odds ratios of 0.91 (0.75 to 1.10) for covid-19 vaccination in the previous three weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous five weeks, showing no

evidence of an increased risk for early pregnancy loss after covid-19 vaccination.⁶⁹

Six studies evaluated the risk of fetal anomalies after maternal vaccination (table 3).^{57 58 61 70 71 77} A large Israeli study of 16 738 infants prenatally exposed to the Pfizer vaccine compared with 7452 unexposed infants did a subgroup analysis among newborns exposed to first trimester vaccination (n=2021) versus unexposed newborns (n=3580) and found no difference in congenital anomalies (risk ratio 0.69, 95% confidence interval 0.44 to 1.04).⁶¹ Additionally, the risk for major heart malformations was lower among the exposed group (risk ratio 0.46, 0.24 to 0.82). Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluating the association of covid-19 vaccination during early pregnancy with risk of congenital fetal anomalies identified an anomaly in 27 (5.1%) of 534 unvaccinated people versus 109 (4.2%) of 2622 people who received at least one dose of vaccine (P=0.35).⁷⁷ Importantly, after control for potential confounders such as hemoglobin A_{1c} level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, 0.72 to 1.54).

We identified nine studies evaluating the risk of stillbirth after covid-19 vaccination.^{38 49 62 64 70-72 74 75} None found an increased risk; however, given the rarity of stillbirth as an event, large studies will be needed to evaluate this risk adequately. In the largest study (n=28 506), no difference was seen in risk of stillbirth after vaccination (2.1 v 1.4 per 100 000 pregnancy days at risk in vaccinated compared with unvaccinated; adjusted hazard ratio 0.86, 0.63 to 1.17).⁷⁴ The small number of stillbirths meant that the study could not explore the risk of stillbirth according to vaccination by pregnancy trimester, number of doses, or vaccine type. A recent systematic review and meta-analysis including five of these studies found that the risk of stillbirth was significantly lower in those vaccinated in pregnancy by 15% (pooled odds ratio 0.85, 0.73 to 0.99).⁸⁰

Twelve studies evaluated the risk of preterm birth after maternal covid-19 vaccination, and the data are reassuring.^{36 38 39 42 50 61 64 70-74} One retrospective study of the Pfizer vaccine in Israel found the overall rate of preterm birth to be 5.5% in the vaccinated group compared with 6.2% in the unvaccinated group (P=0.31); however, people vaccinated in the second trimester of pregnancy (n=964) were more likely to have a preterm birth than those vaccinated in the third trimester (n=1329) (8.1% v 6.2%; P<0.001).⁷² This association persisted after adjustment for potential confounders (adjusted odds ratio 1.49, 1.11 to 2.01). The authors note that no preterm births were seen within two weeks after second trimester vaccination and that most of the preterm births were late preterm, suggesting that unmeasured confounding might have contributed to the results. A larger retrospective study in the US

did not find an increased risk of preterm birth with maternal vaccination (4.9% v 7.0%; adjusted hazard ratio 0.91, 0.82 to 1.01).⁷³ Additionally, no increased risk of preterm birth was seen in the very large cohort study in Norway and Sweden, including no difference between second and third trimester vaccination.⁷⁴

Nine studies evaluated NICU admission rates after maternal vaccination, and none identified an increased risk.^{36 38 42 50 57 64 70 74 78} The largest study found that overall rates of adverse newborn outcomes were lower among those born to people vaccinated during pregnancy versus those vaccinated afterwards, including lower NICU admission (11.0% v 13.3%; adjusted risk ratio 0.85, 0.80 to 0.90).⁷⁸ Additionally, compared with the 30 115 mothers who were never vaccinated, no significantly increased risks of any outcomes were seen in those vaccinated during pregnancy, and NICU admission (11.0% v 12.8%; adjusted risk ratio 0.92, 0.87 to 0.97) was significantly lower among those who were vaccinated during pregnancy.

On the basis of review of available data, no increased risk of adverse pregnancy outcomes was observed among people vaccinated against SARS-CoV-2 during pregnancy, supporting recommendations for vaccination of pregnant patients against SARS-CoV-2. Vaccine safety concerns have been a significant barrier to vaccine acceptance in pregnancy; thus, highlighting the amount of accumulated data is important.

Covid-19 vaccine side effects in pregnancy

We identified 12 studies evaluating adverse effects after maternal covid-19 vaccination.^{37-40 42 44 55 58 71 81-83} In general, symptoms after covid-19 vaccination are usually mild to moderate and occur within the first three days after vaccination. Most occur the day after vaccination and resolve within one to two days. The second dose is associated with more frequent and severe symptoms. The vaccine side effect profile in pregnancy seems to be similar to that in non-pregnant people, with pain at the injection site, fatigue, headache, and myalgia being the most frequent symptoms.^{37 38 42 55 71} Although routine prophylaxis with acetaminophen is not recommended in some countries, pregnant patients should take acetaminophen if they experience fever after vaccination. Severe allergic reactions are rare following covid-19 vaccination in non-pregnant patients (4.7 per million for Pfizer-BioNTech and 2.5 per million for Moderna). Anaphylaxis following vaccination in pregnancy should be managed the same as in non-pregnant patients.²¹

A large prospective cohort study including 7809 pregnant people found that covid-19 vaccines were well tolerated among people who were pregnant, lactating, or planning pregnancy. Odds of several reactions were decreased among people who were pregnant, such as fever after Pfizer dose 2 (odds ratio 0.44, 0.38 to 0.52; P<.001) and after Moderna dose 2 (0.48, 0.40 to 0.57; P<.001)

compared with those who were neither pregnant nor lactating.⁵⁵ The frequency of complaints after vaccination was similar to that observed in non-pregnant patients, and reports of adverse outcomes were infrequent. Additionally, a prospective study of 83 vaccinated pregnant women who were age matched with 166 vaccinated female non-pregnant controls found the frequency of complaints following vaccine administration did not differ between pregnant and non-pregnant patients (18.1% v 16.9%; P=0.20).⁸² However, pregnant patients were more likely to report fever (4.8% v 0.6%; P=0.04) and gastrointestinal symptoms (4.8% v 0%; P=0.01). This could reflect differences in the physiologic responses to the vaccines in pregnancy. One study used data from the “v-safe after vaccination health checker” surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) to characterize the initial safety of mRNA covid-19 vaccines in pregnancy.⁷¹ Local and systemic reactogenicity was compared between people who identified as pregnant and non-pregnant women. The study found small differences in reporting frequency between pregnant people and non-pregnant women observed for specific reactions (injection site pain was reported more frequently in pregnancy, and other systemic reactions were reported more frequently among non-pregnant women), but the overall reactogenicity profile was similar. None of the available data indicate obvious increased adverse effects or safety concerns with use of covid-19 vaccines in pregnancy.

Covid-19 vaccine hesitancy in pregnancy

The search identified 42 articles evaluating vaccine hesitancy in pregnancy in the English language from around the world. Table 4 outlines the studies with either positive or negative associations with willingness or decision for vaccination in pregnancy; three additional studies did not fit these criteria but discussed factors associated with vaccine uptake.¹¹⁵⁻¹¹⁷ Factors positively associated with vaccine willingness/uptake in pregnancy tended to be the same around the globe, including older maternal age, higher education, previous influenza vaccine uptake, higher level of trust in the healthcare system, increased perceived risk of covid-19, fertility treatments, urban living, and higher socioeconomic status (table 4). Factors associated with a lower likelihood of vaccination during pregnancy included younger age, lower education/socioeconomic status, and lack of adherence to influenza vaccination recommendations. Pregnancy itself was found to be negatively associated with vaccine acceptance in several studies when a non-pregnant cohort was used for comparison.

Data from Vaccine Safety Datalink, a collaboration between the Centers for Disease Control and Prevention (CDC) and multiple integrated health systems, analyzed receipt of at least one dose of any covid-19 vaccine in 135 968 pregnant women

between 14 December 2020 and 8 May 2021.⁹¹ Vaccination increased with age, with highest rates of at least one dose observed among women aged 35-49 years (22.7%) and lowest rates among those aged 18-24 years (5.5%). Receipt of at least one dose was highest among Asian women (24.7%), followed by white (19.7%) women, and lowest among Black (6.0%) and Hispanic (11.9%) women. One study found that the impact of education and influenza vaccination history on vaccine acceptance varied depending on race, suggesting that different public health messaging might be appropriate for Black or African-American women because of their lived experiences with systemic racism and mistrust in the healthcare system.⁹⁰

Another emerging theme from the data was the importance of counseling from healthcare providers. Previous data show that the recommendation and offer of the influenza vaccine by a healthcare provider are critical for uptake in pregnancy.¹¹⁸ Several studies found that a provider’s recommendation was positively associated with covid-19 vaccination.^{87 89 98 110} A large nationwide prospective study in the US was used to characterize vaccination rates and acceptance during pregnancy in the first six months of vaccine rollout.⁸⁹ Among 2506 pregnant respondents, 57.4% had received one dose of covid-19 vaccination in pregnancy. In an adjusted model, the predictors of lower odds of vaccination included Black race (21.8%) compared with white race (58.2%) (P<0.001); being counseled about vaccination by a provider was a strong predictor of getting vaccinated (69.4%) compared with no counseling (38.5%) (P<0.001). The best methods to provide educational resources to providers and to ensure that covid-19 vaccination recommendations are routinely discussed with obstetric patients should be a research priority. Ensuring that providers have up to date information on the maternal and neonatal safety of covid-19 vaccines in pregnancy is critical, as this is needed to help guide their counseling.

In a large multi-country study of 17 871 women, including 5282 who were pregnant, conducted before vaccines were available, 2747 (52.0%) pregnant women and 9214 (73.4%) non-pregnant women indicated an intention to receive a covid-19 vaccine.¹⁰² The top three reasons why pregnant women would decline vaccination even if the vaccine were safe and free were that they did not want to expose their developing baby to any possible harmful side effects (65.9%), they were concerned that approval of the vaccine would be rushed for political reasons (44.9%), and they would like to see more safety and effectiveness data during pregnancy (48.8%). Vaccine acceptance was lowest in Russia, the US, and Australia. The strongest predictors of vaccine acceptance included confidence in vaccine safety or effectiveness, worrying about covid-19, belief in the importance of vaccines to their own country, compliance with mask guidelines, trust of public health agencies/health science, and attitudes toward routine vaccines.

Table 4 | Covid-19 vaccine hesitancy in pregnancy

Author; study design	Population	Positive association with vaccination or willingness to be vaccinated	Negative association with vaccination or willingness to be vaccinated
United Kingdom			
Blakeway H, 2022 ⁵⁷ ; retrospective cohort study	Pregnant vaccinated, n=140; pregnant unvaccinated, n=1188	Pre-pregnancy diabetes	Younger women; non-white ethnicity; lower socioeconomic background
Anderson E, 2021 ⁸⁴ ; qualitative interview study	Pregnant, n=31	-	Concern vaccine riskier than covid
United States			
Sznajder K, 2022 ⁸⁵ ; secondary analysis	Pregnant, n=196	Received influenza vaccine in previous year; full time employment; feeling overloaded	
Battarbee A, 2022 ⁸⁶ ; cross sectional survey	Pregnant, n=915	Received influenza vaccine in previous season	Hispanic and Black women
Keifer M, 2022 ⁸⁷ ; cross sectional survey	Pregnant, n=435; postpartum, n=21	Higher level of education; older age; Asian race; reporting a friend or family member who received covid-19 vaccine; planning or had Tdap vaccine; receipt of influenza vaccine in current year; concern about covid-19; discussing vaccine with obstetric provider	Non-Hispanic Black; young age; public health insurance; tobacco use in pregnancy; any drug use; parity
Wang T, 2021 ⁸⁸ ; cross sectional cohort; electronic survey	Healthcare workers, n=83; pregnant, n=20; lactating, n=19; would like to become pregnant soon, n=47	Increased perceived risk of covid; agreed covid-19 vaccine was safe and effective in pregnancy	Pregnancy; concern for fertility
Huddleston H, 2022 ⁸⁹ ; national prospective cohort study (ASPIRE)	Pregnant, n=2506	Higher income; higher education; living in metropolitan area; worry about covid-19; being counseled about vaccination by provider	Black race; being counseled by provider not to vaccinate
Levy A, 2021 ⁹⁰ ; survey study	Pregnant, n=662	Trust in information received about vaccinations	Younger age; Black or African-American race; Hispanic ethnicity; less education; declining influenza vaccine; concern for fetal safety
Razzaghi H, 2021 ⁹¹ ; Vaccine Safety Datalink (VSD)	Pregnant, n=135 968	Older age; Asian women	Black women; Hispanic women
Sutton D, 2021 ⁹² ; online survey	Respondents, n=1012; pregnant, n=656; lactating, n=122	-	Pregnancy; non-white race; Spanish speaking
Theiler R, 2021 ⁶⁴ ; cohort study	Pregnant; vaccinated, n=140; unvaccinated, n=1862	Older age; higher maternal education; non-smoker; fertility treatment; lower gravity	-
Israel			
Rottensteich M, 2022 ⁵⁰ ; multicenter retrospective database study	Pregnant; vaccinated, n=712; unvaccinated, n=1063	Older age; fertility treatment; previous cesarean delivery; previous miscarriage	-
Bleicher I, 2021 ⁵⁸ ; prospective observational study	Pregnant, n=313	Flu vaccine in current or previous year; medical employee	Concern about lack of safety data in pregnancy; fear of short and long term side effects; history of covid infection; no comorbidities
Saleh O, 2022 ⁹³ ; online survey	Women 6 months before or after giving birth, n=410; pregnant, n=293; post partum, n=117	Jewish religion; academic education; employment; urban	-
Taubman-Ben-Ari O, 2022 ⁹⁴ ; online survey	Jewish pregnant women, n=187; Arab pregnant women, n=673	Lower levels of psychological distress in Arab women	-
Wainstock T, 2021 ⁷⁶ ; retrospective cohort study	Pregnant; vaccinated, n=913; unvaccinated, n=3486	Older age; fertility treatment; sufficient prenatal care; higher socioeconomic position	-
Ethiopia			
Mose A, 2021 ⁹⁵ ; cross sectional survey	Pregnant, n=396	Maternal age 34-41; educational status; good knowledge; good practice with covid-19 guidelines	-
Hailemariam S, 2021 ⁹⁶ ; cross sectional survey	Pregnant, n=412	Urban residence; secondary and higher education; compliance with covid-19 guidelines; good perception toward covid vaccine	-
Taye E, 2022 ⁹⁷ ; cross sectional survey	Pregnant, n=360; post partum, n=159	Urban residence; favorable attitude toward covid vaccine; worried about covid-19 disease	-
France			
Egloff C, 2022 ⁹⁸ ; cross sectional survey	Pregnant, n=664	Older; higher education; multiparty; having discussed vaccination with a care giver; acceptance of influenza vaccine	-
Deruelle P, 2021 ⁹⁹ ; online survey	n=1416; obstetrician/gynecologist, n=749; midwife, n=598; general practitioner, n=69	Being an obstetrician; working in a group; usually offering flu vaccine; wanting to be vaccinated	-
Italy			
Carbone L, 2021 ¹⁰⁰ ; multicenter cross sectional study	Pregnant, n=119; post partum, n=23	-	Pregnancy
Mappa I, 2021 ¹⁰¹ ; prospective observational study	Pregnant, n=161	-	Lower education; lower employment level
16 countries			
Skjefte M, 2021 ¹⁰² ; cross sectional survey	Pregnant, n=5294; non-pregnant mothers, n=12 562	Mexico; India; confidence in vaccine safety and efficacy; importance of vaccines/mass vaccination in their own country; worry about covid-19; trust of public health/science; compliance with mask guidelines	United States; Australia; Russia; younger age; lower income; lower education not married; no health insurance

(Continued)

Table 4 | Continued

Author; study design	Population	Positive association with vaccination or willingness to be vaccinated	Negative association with vaccination or willingness to be vaccinated
Australia			
Bradfield Z, 2021 ¹⁰³ ; national cross sectional online study	Doctors, n=58; midwives, n=391; midwifery students, n=78; women, n=326	Doctors	Midwives
China			
Tao L, 2021 ¹⁰⁴ ; multicenter cross sectional study	Pregnant, n=1392	Younger age; western region; low level of education; late pregnancy; high knowledge score on covid-19; high level of perceived susceptibility; low level of perceived barriers; high level of perceived benefit; high level of perceived cues to action	-
Czech Republic			
Riad A, 2021 ¹⁰⁵ ; cross sectional survey	Pregnant, n=278; lactating, n=84	Third trimester > 1st trimester; older age; higher education; trust in industry and healthcare professionals	-
Germany			
Schaal N, 2021 ¹⁰⁶ ; cross sectional survey	Pregnant, n=1043; lactating, n=1296	Anxiety about getting infected	-
Greece			
Daskalakis G, 2021 ¹⁰⁷ ; electronic survey	Obstetricians, n=504; midwives, n=214; pediatricians, n=176; other healthcare providers, n=332	-	Non-medical, non-midwife/nurse professional, non-involvement in higher education; lack of adherence for vaccinations of pregnant women against flu/pertussis; healthcare provider not vaccinated
Ireland			
Geoghegan S, 2021 ¹⁰⁸ ; survey	Pregnant, n=300	Later gestational age; age 30-35	-
Japan			
Hosokawa Y, 2022 ¹⁰⁹ ; cross sectional survey	Pregnant, n=1791		Lack of trust in government
Poland, Ukraine			
Januszek S, 2022 ¹¹⁰ ; cross sectional survey	Pregnant in Poland, n=150; pregnant in Ukraine, n=150	Medical consultation; Polish > Ukrainian	Fear of harming fetus; complications in pregnancy
Qatar			
Mohan S, 2021 ¹¹¹ ; nationwide online cross sectional study	Pregnant or lactating, n=341	-	Concern about vaccine safety; worry about vaccine problems; feeling natural immunity is better/safer
Romania			
Citu I, 2022 ¹¹² ; cross sectional survey	Pregnant, n=184; non-pregnant, n=161	-	Not being afraid of covid; below average income; trusting rumors in social media; not believing in covid virus or vaccines; vaccination non-believer
Saudi Arabia			
Samannodi M, 2021 ¹¹³ ; cross sectional survey	Pregnant or planning pregnancy, n=214; other women, n=217	-	Pregnancy or planning pregnancy
Switzerland			
Stuckelberger S, 2021 ¹¹⁴ ; cross sectional survey	Pregnant, n=515; lactating n=1036	Age >40; higher education; influenza vaccine in previous year; third trimester; having obstetrician as primary healthcare practitioner	-

Over the past year, substantial data have been generated on covid-19 vaccines in pregnancy. Concerns for fetal/neonatal safety due to lack of data on safety of the vaccines in pregnancy are often cited as justification for declining the vaccine during pregnancy. The inclusion of pregnant people in vaccine research is of crucial importance to help to increase knowledge for this population.

Guidelines

WHO states that pregnant women can receive covid-19 vaccines and, if not already vaccinated, should have access to WHO Emergency Use Listing approved vaccines, as the benefits of vaccination during pregnancy outweigh potential risks.¹¹⁹ WHO recommends the Johnson & Johnson-Janssen, Moderna, Novavax, Oxford-AstraZeneca, and Pfizer-BioNTech vaccines and permits Sinopharm,

BIBP-CorV, Sinovac CoronaVac, and Bharat Biotech Covaxin. In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) and Joint Committee on Vaccination and Immunisation (JCVI) state that: "COVID-19 vaccines are strongly recommended in pregnancy."¹²⁰ The RCOG prefers that pregnant women be offered the Pfizer-BioNTech or Moderna mRNA vaccines, where available, given the greater amount of data on this vaccine type and that current data have not raised any safety concerns. However, women who have already had one dose of the Oxford-AstraZeneca vaccine are advised to complete vaccination with a second dose of the same vaccine.

In the US, the CDC, the ACOG, and the SMFM all recommend that people who are pregnant get vaccinated and stay up to date with their covid-19 vaccines, including getting a booster shot.^{20 21 121} Overall, the CDC states a preference for mRNA

covid-19 vaccines over the Johnson & Johnson-Janssen vaccine for primary and booster vaccination; however, the latter vaccine may be considered in certain situations such as an allergic reaction, limited access to mRNA vaccines, or patient preference; this includes during pregnancy.

As of 12 March 2022, China's position is that covid-19 vaccination during pregnancy is not recommended, and vaccination while lactating is recommended for some or all.¹⁹ In India, with approximately 25 million births annually, the currently available covid-19 vaccines are Covishield and Covaxin.¹⁹ At present, the recommendations from the Ministry of Health and Family Welfare, Government of India, state that pregnancy and lactation are contraindications to covid-19 vaccinations.¹²² However, the Federation of Obstetric and Gynaecological Societies of India's position statement on covid-19 vaccination for pregnant and breastfeeding women states that protection from covid-19 vaccination should extend to pregnant and lactating women, given that the benefits seem to far outweigh any theoretical and remote risks of vaccination.¹²³ The International Society of Infectious Diseases in Obstetrics and Gynaecology advises policy makers and societies to prioritize pregnant women to receive vaccination against SARS-CoV-2 and favors the mRNA vaccines until further safety information becomes available.¹²⁴

Conclusions

Covid-19 vaccination is the safest and most effective way for people who are pregnant to protect themselves and their babies against severe covid-19 disease. Available data do not support an increased risk of adverse outcomes following covid-19 vaccination in pregnancy, so vaccination should be recommended as the benefits of vaccination during pregnancy seem to outweigh any potential risks. The immunogenicity of vaccinations in pregnancy seems to be similar to that in the non-pregnant population; however, the optimal timing of vaccination in pregnancy for neonatal/infant benefit remains uncertain. Additional information on non-mRNA vaccines, vaccination early in pregnancy, and longer term infant outcomes are also needed. Given that pregnant people are at increased risks for severe complications from covid-19, increasing the data

RESEARCH QUESTIONS

- Should the covid-19 vaccine schedule in pregnancy be different from that in non-pregnant people? Does an optimal gestational timing of covid-19 vaccination in pregnancy exist?
- What are the degree and extent of neonatal/infant protection with maternal covid-19 vaccination in pregnancy?
- What are the most effective strategies to reduce vaccine hesitancy in pregnancy?
- Do perinatal outcomes differ among the various covid-19 vaccines?

PATIENT INVOLVEMENT

We provided an initial draft of the manuscript and outline of the key points of the paper to a patient who chose to be vaccinated in pregnancy and one who opted to wait until post partum. They both expressed concern about unknown fetal risks with receiving a novel vaccine in pregnancy. The patient who declined vaccination stated that she did not want to be responsible for choosing anything that might increase the risk for adverse perinatal outcomes for her baby and she would proceed with vaccination only once pregnancy specific data were available. The patient who got vaccinated and also boosted in pregnancy reported that a key factor in her decision was previous history with always receiving recommended vaccinations before covid-19 and trusting medicine at baseline. Both patients emphasized the importance of receiving direct vaccine counseling about their specific pregnancy from their obstetric healthcare provider. On the basis of these observations, we modified the manuscript to ensure a focus on perinatal outcomes and vaccine hesitancy and also to acknowledge the importance of counseling by the obstetric provider on covid-19 vaccination in pregnancy.

and knowledge surrounding vaccination in this population is important to help to reduce vaccine hesitancy. Along with more data, directed personal vaccine counseling by obstetric providers to pregnant patients may also improve vaccination rates. To meet all these goals, pregnant people around the world must be prioritized in covid-19 vaccine research.

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