Covid-19 vaccination in pregnancy

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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 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.

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 Index of Nursing and Allied Health), Embase, MEDLINE via PubMed, and Web of Science Classic
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-
from SARS-CoV-2 infection, so providing protection and Gynecologists (ACOG) and the Society for including the American College of Obstetricians during pregnancy likely also varies considerably. In contrary to vaccination in this population. Given the people, whereas 15 countries specifically recommend vaccination for some or all pregnant or lactating public health policies regarding recommendations about covid-19 vaccines for pregnant and lactating people, 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; 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.

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. 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, and the AstraZeneca vaccine was 70.4% effective after two doses. 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. 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
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 33 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

| 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 | 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.23 |
| mRNA-1273 | Moderna | 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.30 |
| Ad26.Cov2.S | Johnson & Johnson-Janssen | Recombinant replication incompetent human adenovirus vector encoding SARS-CoV-2 spike protein | 5×10¹⁷ 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). |
| ChAdOx1 (AZS1222) | Oxford-AstraZeneca | Recombinant replication deficient chimpanzee adenoviral vector encoding SARS-CoV-2 spike protein | 5×10¹⁷ 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.
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 |
|----------------------|--------------|------------------|--------------------------------------|-----------------------------|------------------------|
| Alyeo C, 2021; 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 | 23.2 (range 16-32.1) | Fc receptor antibody concentrations were significantly lower in pregnancy than 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 FcyRIIIa binding in cord |
| Beharier O, 2021; 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 IgG51 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 vs natural infection (P<0.001) |
| Ben-Mayor B, 2022; prospective cohort study | Pfizer: 1st dose, n=19; 2nd dose, n=39 | Vaccinated n=58 | 1st dose 34.5, 2nd dose 37.141 | 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 (p=0.857; R2 linear=0.719; P=0.001) |
| Bookstein P, 2021; 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 women had a lower IgG0.41 (IQR 0.31-0.45) vs 0.40 (0.32-0.47) U/mL (P=0.82) at 2 months; 1083 (896-1468) vs 1114 (909-1482) U/mL (P=0.35) at 4 months | Not evaluated |
| Citu I, 2022; observational case-control study | Pfizer: Janssen | Vaccinated, n=27; unvaccinated, n=608; vaccinated without covid-19 history, n=173; unvaccinated without covid-19 history, n=529; non-pregnant, n=227 | Third trimester | Seronegative (n=173) vs seropositive (n=54) pregnant patients: median anti-S IgG 0.41 (IQR 0.31-0.45) vs 1.45 (0.2-208.1) U/mL (P<0.001) before vaccination; 1697 (393-2115) vs 145.71 (126.28-15337) U/mL (P<0.001) at 2 months; 1083 (896-1468) vs 104.7 (9043-12571) U/mL (P<0.001) at 4 months. Pregnant (n=173) vs non-pregnant (n=173) without history of SARS-CoV-2: anti-S IgG 0.41 (0.31-0.45) vs 0.40 (0.32-0.47) U/mL (P<0.001) before vaccination; 1697 (1393-2115) vs 1705 (1452-2179) U/mL (P=0.82) at 2 months; 1083 (896-1468) vs 1114 (909-1482) U/mL (P=0.35) at 4 months | Not evaluated |
| Collier A, 2021; prospective cohort study | Pfizer, n=11; Moderna, n=9 | Vaccinated, n=103; unvaccinated, n=608; vaccinated without covid-19 history, n=173; unvaccinated without covid-19 history, n=529; non-pregnant, n=227 | 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 13.21; pregnant vaccinated, median neutralizing titer 910; pregnant vaccinated, median neutralizing titer 148; 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 ± 14953). Median cord neutralization titer lower than maternal blood (324 vs 1016) |
| Gloeckner S, 2022; observational cohort study | Prime vaccine: AstraZeneca, boost vaccine 12 weeks later, Pfizer or Moderna | Pregnant, n=5; 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; prospective cohort study | Pregnant: 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, median 5.95 (IQR 4.68-5.89); non-pregnant, median 5.62 (4.77-5.98); P=0.24. All titles 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 61.2-192], cord sera, 52.3 [11.7-69.6]; P=0.05) |
| Kashani-Ligumsky L, 2021; 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 neutral antibody titers higher in vaccinated (22.5 U/mL) vs infected (8.37 U/mL) (P=0.05) |
| Kugelman N, 2021; 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 –1.2% to 21.4%); P=0.002. Change in maternal antibody level per 1 year increase in maternal age: 3.1% (–5.3% to 0.9%); P=0.007 | 100% positive for SARS-CoV-2 IgG. IgG titer 2.6 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 |
|----------------------|--------------|------------------|-------------------------------------|-----------------------------|------------------------|
| Liu M, 2021; 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 (91%). 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 (β=0.2; 95% CI 0.1 to 0.2). Second dose before delivery was associated with increased infant IgG levels (β=19.0, 7.1 to 30.8). Latency from vaccination to delivery was associated with increased infant IgG levels (β=2.9, 0.7 to 5.1) |
| Nir O, 2021; 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: 25/28 (89%) | 98.3% positive for SARS-CoV-2 IgG. SARS-CoV-2 IgG: 20.2 (12.7-29.0) in vaccinated v 3.2 (0.5-6.1) in recovered (P<0.001) |
| Prabhu M, 2021 | Pfizer | One dose, n=5; 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) |
| Rottenstreich A, 2021; prospective cohort study | Pfizer, n=20 | Fully vaccinated, n=20 | All 3rd trimester | SARS-CoV-2 antiS and anti-RBD: 100% | SARS-CoV-2 antiS 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 (g=0.27; P=0.001 and g=0.27; P=0.001, respectively). Cord blood titers directly correlated with increasing time from 1st vaccine dose (P=0.71; P=0.001 and P=0.06; P=0.004, respectively) |
| Rottenstreich A, 2022; 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) | 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) |
| Rottenstreich M, 2022; prospective cohort study | Pfizer | Vaccinated, n=402 | 1st trimester: anti-S IgG 76 AU/mL; anti-RBG IgG 478 AU/mL. 2nd trimester: anti-S IgG 126 AU/mL; anti-RBG IgG 585 AU/mL. Vaccine in 1st trimester with booster dose in 3rd trimester: anti-S IgG 1665 AU/mL; anti-RBG IgG 5946 AU/mL | 100% SARS-CoV-2 anti-S and anti-RBD. Neutralizing antibodies placental transfer ratio positively associated with longer duration from vaccination (r=0.77; P=0.001) |
| Shanes E, 2021; cohort study | Pfizer | n=49; Moderna, n=25; mRNA unknown type, n=9 | All 3rd trimester | Not evaluated | (Continued)
Table 2 | Continued

| Author; study | Gestational age at vaccination, weeks | Seropositive maternal blood | Seropositive cord blood |
|---------------|---------------------------------------|-----------------------------|------------------------|
|                | Wild type variant: SARS-CoV-2 neutralizing IgG | with a boosting effect of a third vaccine dose.49 | found considerable antibody waning throughout pregnancy in those vaccinated in the first trimester, with a boosting effect of a third vaccine dose.49 |
|                | Pfizer, n=36; Moderna, n=26; Janssen, n=10 | 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 37 38 40 41 42 43 44 45 46 47 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.45-53 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.46 47 48 49 50 51 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.54 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.55 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

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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 overwhelmingly 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.58 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).52 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[11]; USA; case-control surveillance study | Pfizer, n=8267; Moderna, n=6313; Janssen, n=528 | Pregnant vaccinated, n=15108; pregnant unvaccinated, n=90338 | SAB: 1128/13160 (8.6%) SAB occurred within 28 days of vaccination; 20 139/250949 (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[12]; 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 12.6% (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[13]; Norway; case-control study | Pfizer, n=790; Moderna, n=137; AstraZeneca, n=76 | Vaccinated, n=958; unvaccinated, n=13613 | 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% |
| Trostle R, 2021[14]; USA; case series | Pfizer, n=332; Moderna, n=92 | Vaccinated, n=424; delivered liveborn infant, n=85 | 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=0.61). 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[15]; USA; 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: vaccinated 9.4%; FGR/SGA 3.2%; major congenital anomaly 2.2%; SAB 12.6%; stillbirth 0.1%; neonatal death 0% |
| Theiler R, 2021[16]; 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 34.1%; unvaccinated 29.8% (P=0.65). Stillbirth: vaccinated 0%; unvaccinated 0.3% (P=1.0). NICU admission: vaccinated 0.7%; 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[17]; Israel; prospective cohort study | Pfizer or Moderna | Vaccinated, n=2305; unvaccinated, n=1313 | 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=0.01). 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[18]; USA; observational retrospective cohort study | Pfizer, n=5478; Moderna, n=4162; Janssen, n=424 | Vaccinated, n=10064; unvaccinated n=36015 | Preterm birth: vaccinated 10.8%; unvaccinated 9.2% (P=0.06). FGR/SGA: vaccinated 8.2%; unvaccinated 8.2% (P=0.24). Cesarean delivery: vaccinated 11.5%; unvaccinated 13.0% (P=0.61) |
| Goldstein L, 2022[19]; Israel; cohort study | Pfizer | Infants of unvaccinated mothers, n=7591; infants of vaccinated mothers, n=16697 | 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[20]; 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, 2022[21]; 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, 2022[22]; 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[23]; Norway; Sweden; registry based retrospective cohort study | Pfizer, n=20424; Moderna, n=7607; AstraZeneca, n=475 | Vaccinated, n=28506; unvaccinated, n=129015 | Preterm birth: vaccinated 6.2 v unvaccinated 4.9 per 10 000 pregnancies 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 pregnancies 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, 2022[24]; 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[25]; 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) |
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.80 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 (9 133 vaccinated; 3 486 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 16738 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 A1c 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 62 64 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<0.001) and after Moderna dose 2 (0.48, 0.40 to 0.57; P<0.001).
compared with those who were neither pregnant nor lactating.\textsuperscript{35} 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% \textit{v} 16.9%; \textit{P}=0.20).\textsuperscript{82} However, pregnant patients were more likely to report fever (4.8% \textit{v} 0.6%; \textit{P}=0.04) and gastrointestinal symptoms (4.8% \textit{v} 0%; \textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{118} Several studies found that a provider’s recommendation was positively associated with covid-19 vaccination.\textsuperscript{87, 98, 110} A large nationwide prospective study in the US was used to characterize vaccine rates and acceptance during pregnancy in the first six months of vaccine rollout.\textsuperscript{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%) (\textit{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%) (\textit{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.\textsuperscript{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; retrospective cohort study | Pregnant, n=140; pregnant unvaccinated, n=1188 | Pre-pregnancy diabetes | Younger women; non-white ethnicity; lower socioeconomic background |
| Anderson E, 2021; qualitative interview study | Pregnant, n=31 | - | Concern vaccine riskier than covid |
| **United States**    |            |                                                |                                                  |
| Sznaider K, 2022; secondary analysis | Pregnant, n=196 | Received influenza vaccine in previous year; full time employment; feeling overloaded | Hispanic and Black women |
| Baltarbee A, 2022; cross sectional survey | Pregnant, n=915 | Received influenza vaccine in previous season | Hispanic and Black women |
| Kefer M, 2022; 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 I, 2021; 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; 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; 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; Vaccine Safety Datalink (VSD) | Pregnant, n=135,968 | Older age; Asian women | Black women; Hispanic women |
| Sutton D, 2021; online survey | Respondents, n=1012; pregnant, n=656; lactating, n=122 | - | Pregnancy; non-white race; Spanish speaking |
| Theier R, 2021; cohort study | Pregnant; vaccinated, n=140; unvaccinated, n=1862 | Older age; higher maternal education; non-smoker; fertility treatment; lower gravity | - |
| **Israel**           |            |                                                |                                                  |
| Rottensteich M, 2022; multicenter retrospective database study | Pregnant; vaccinated, n=712; unvaccinated, n=1063 | Older age; fertility treatment; previous cesarean delivery; previous miscarriage | - |
| Bleicher L, 2021; 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; 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; online survey | Jewish pregnant women, n=187; Arab pregnant women, n=673 | Lower levels of psychological distress in Arab women | - |
| Wainstok T, 2021; retrospective cohort study | Pregnant; vaccinated, n=913; unvaccinated, n=3486 | Older age; fertility treatment; sufficient prenatal care; higher socioeconomic position | - |
| **Ethiopia**         |            |                                                |                                                  |
| Mose A, 2021; cross sectional survey | Pregnant, n=396 | Maternal age 34-41; educational status; good knowledge; good practice with covid-19 guidelines | - |
| Hailemariam S, 2021; 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; cross sectional survey | Pregnant, n=360; post partum, n=159 | Urban residence; favorable attitude toward covid vaccine; worried about covid-19 disease | - |
| **France**           |            |                                                |                                                  |
| Egoiff C, 2022; cross sectional survey | Pregnant, n=664 | Older; higher education; multiparty; having discussed vaccination with a care giver; acceptance of influenza vaccine | - |
| Deruelle P, 2021; 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; multicenter cross sectional study | Pregnant, n=119; post partum, n=23 | - | Pregnancy |
| Mappa I, 2021; prospective observational study | Pregnant, n=161 | - | Lower education; lower employment level |
| **16 countries**     |            |                                                |                                                  |
| Skjefte M, 2021; cross sectional survey | Pregnant, n=5,294; 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)
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, BBP-CoV, 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 vaccines.
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 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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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.

RESEARCH QUESTIONS
• Should the covid-19 vaccine schedule in pregnancy differ 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?
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