COVID-19 disease and vaccination in pregnant and lactating women

Marco A. P. Safadi1 | Julia Spinardi2 | David Swerdlow3 | Amit Srivastava4

1Department of Pediatrics, Santa Casa de Sao Paulo School of Medical Sciences, Sao Paulo, Brazil
2Vaccine Medical Affairs – Emerging Markets, Pfizer Inc, Sao Paulo, Brazil
3Pfizer Vaccines, Collegeville, Pennsylvania, USA
4Vaccines, Medical Development, Scientific and Clinical Affairs, Pfizer Inc, Cambridge, Massachusetts, USA

Correspondence
Amit Srivastava, Pfizer Inc, 300 Technology Square, 3rd Floor, Cambridge, MA 02139, USA. Email: Amit.K.Srivastava@pfizer.com

Funding information
Pfizer Inc.

Abstract

Background: More than 325,000 cases of coronavirus disease 2019 (COVID-19) have been reported among pregnant women in the Americas.

Aims: This review examines the impact of COVID-19 in pregnant women and describes available evidence on the safety, effectiveness, and immune response(s) to vaccination among pregnant and lactating women.

Content: Multiple studies indicate that pregnant women are more susceptible to adverse COVID-19 outcomes, including hospitalization, intensive care unit admission, and invasive ventilation than non-pregnant women with COVID-19. Furthermore, COVID-19 in pregnancy is associated with adverse maternal and neonatal outcomes. Adverse COVID-19 outcomes appear to disproportionately affect pregnant women from low- and middle-income countries, likely reflecting inequities in access to quality healthcare. Despite the absence of safety and efficacy data from randomized clinical trials in this subpopulation, observational studies and data from pregnancy registries thus far have demonstrated that vaccination of pregnant or lactating women against COVID-19 is safe, effective, and results in robust immune responses including transfer of antibodies to the newborn via the placenta and breast milk, respectively.

Implications: These data support vaccination recommendations intending to help protect these vulnerable individuals against COVID-19 and its sequelae. Randomized clinical studies will further evaluate the safety and immunogenicity of COVID-19 vaccines in these populations. This review examines the impact of COVID-19 in pregnant women and describes available evidence on the safety, effectiveness, and immune response(s) to vaccination among pregnant and lactating women.

KEYWORDS
COVID-19, COVID-19 vaccines, immunogenicity, lactation, pregnancy, safety, SARS-CoV-2, VACCINATION

1 INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been globally devastating. As of March 16, 2022, there have been > 460 million confirmed COVID-19 cases and > 6 million deaths worldwide.1 Compared with nonpregnant women with COVID-19, infected pregnant women have an increased likelihood of developing severe outcomes, including hospital admission, intensive care unit (ICU) stay, and need for invasive ventilation.2-5 The burden of...
COVID-19 in pregnant women is likely underestimated and varies geographically; adverse pregnancy outcomes are generally more frequent in low- and middle-income countries (LMIC).6–8 COVID-19 vaccines are authorized for general or emergency use globally,9 with >7 billion vaccine doses administered to date.1 As with many early clinical trials, pregnant or lactating women were excluded from COVID-19 vaccine authorization studies10,11; randomized clinical trial data on COVID-19 vaccine safety and efficacy among these groups were thus lacking when vaccine use was first authorized. However, acknowledging the pandemic emergency and the imperative to ensure access of pregnant or lactating women to vaccine-mediated protection against COVID-19, various public health organizations recommend vaccination of these subpopulations.10–12 Nevertheless, vaccination rates among pregnant women remain lower than among nonpregnant women,13 leaving many pregnant women at continued risk of infection and COVID-19.

Several health authorities are monitoring pregnancy outcomes following vaccination through surveillance, including pregnancy registries. These efforts coupled with observational studies have contributed to the modest but growing evidence base concerning COVID-19 vaccine use in pregnancy. This review summarizes the impact of COVID-19 in pregnant/lactating women and describes emerging evidence regarding their immune response(s) to disease and vaccination.

2 | EPIDEMIOLOGY AND OUTCOMES OF COVID-19 DURING PREGNANCY

2.1 | Epidemiology

As of October 28, 2021, a total of 325,344 SARS-CoV-2 infections and 3237 deaths were reported among pregnant women in 33 countries/territories with available information from the World Health Organization (WHO) Americas region.14 Case numbers vary widely between countries, likely reflecting differences in population size and surveillance/reporting. There have been >141,000 known COVID-19 cases and 218 deaths in US pregnant women through November 8, 2021, with approximately equal case numbers in Hispanic/Latina and White/non-Hispanic women.15 Through October 28, 2021, Brazil reported 1283 deaths in pregnant women with COVID-19.14 Inter-country differences in COVID-19–related antepartum and postpartum mortality reflect discrepancies that existed previously,16 with the pandemic and its burden on the healthcare system likely exacerbating underlying healthcare access disparities associated with differential health outcomes. In Brazil, 1031 maternal deaths occurred among the 11,247 cases of COVID-19 severe acute respiratory syndrome in pregnant/postpartum women during March 1, 2020–May 5, 2021 (9.2% case-fatality rate); case-fatality rates were highest during the second trimester (11.4%) and the postpartum period (18.9%).16 Among those who died, 22.5% and 33.5% did not have access to an ICU or invasive ventilator support, respectively. Alarming levels of mortality among SARS-CoV-2–positive pregnant women rose dramatically in 2021 relative to 2020 in many Latin American countries, including Brazil (from 9.0 to 36.4 per 100,000 live new births), Paraguay (from .7 to 60.1), and Colombia (from 7.7 to 24.4), among others.14 The emergence and spread of highly transmissible SARS-CoV-2 variants will likely affect COVID-19 incidence and hospitalization rates. In particular, rapid increases in cases and hospitalizations associated with the Delta variant, including in countries with high vaccine coverage, is concerning.17 The Delta variant was initially identified in July 2020 and by October 26, 2021, was reported in 185 countries.14,17 Preliminary evidence from India and the United Kingdom suggests greater symptom severity and possibly higher mortality rates in pregnant women associated with this variant compared with earlier SARS-CoV-2 strains,18,19 driven perhaps by increased transmissibility relative to the ancestral variant.20 In Mississippi in the United States, an apparent increase in COVID-19–associated deaths among pregnant women was observed after the Delta variant became the predominant strain (pre-Delta period, five deaths per 1000 infections during pregnancy; Delta predominance period, 25 deaths per 1000).21 Similarly, the authors of a recent Brazilian study hypothesized that increased maternal mortality rates in 2021 relative to 2020 may be related to the rise of the Gamma variant.22 During the period of Gamma variant predominance, a higher risk of death and severe COVID-19 outcomes among pregnant and postpartum women was observed in Brazil.23

2.2 | Effect of pregnancy on COVID-19 outcomes

Pregnant women with COVID-19 may have a higher risk of hospital/ICU admission and a greater need for invasive interventions compared with nonpregnant infected women.2–5 A meta-analysis including studies published through October 6, 2020, identified increased risk for ICU admission (odds ratio [OR]; 95% confidence interval [CI]: 2.13; 1.54, 2.95), invasive mechanical ventilation (2.59; 2.28, 2.94), and extracorporeal membrane oxygenation (ECMO; 2.02; 1.22, 2.34), but not receipt of oxygen through a nasal cannula or all-cause mortality, among pregnant women with COVID-19 compared with similarly aged infected nonpregnant women.2 Similarly, a meta-analysis of nine studies published through February 25, 2021, identified increased risks of ICU admission and invasive mechanical ventilation among pregnant relative to nonpregnant women with COVID-19 (Table S1).3 Importantly, analyses that adjusted for age, comorbidity presence, and/or race/ethnicity supported these findings.3,24–26 Severe COVID-19 was also more frequent among pregnant women in several studies.27–29 Studies not supporting this relationship defined “severe” disease inconsistently or based on symptoms rather than morbidity.3,30 Community-based studies can provide information regarding hospitalization risk among alarger group that may be more generalizable to the overall population (Table 1).4,5,26,31,32 In a community-based study in the United Kingdom, Sweden, and United States (not included in Table 1), pregnant and nonpregnant women with COVID-19 had similar symptom severity, although pregnant women more frequently developed severe gastrointestinal symptoms, especially...
| Study          | Setting                                                                 | Relative risk (95% CI)\(^a^\,^b\) | Hospitalization | ICU admission | Invasive/mechanical ventilation | ECMO | Death     |
|---------------|-------------------------------------------------------------------------|-----------------------------------|----------------|--------------|---------------------------------|------|-----------|
| Rios-Silva 2020\(^\text{31}\) | Analysis of data from a national database in Mexico (448 pregnant women, 17 942 nonpregnant women 13 to 49 years of age with COVID-19) | 2.10 (1.82, 2.55)                |                | 10.2% versus 7.4%, \(P = .2\) | 5.1% versus 5.7%, \(P = .7\) |      | .74 (.35, 1.56) |
| Zambrano 2020\(^\text{4}\)   | Analysis of US surveillance data from the CDC (30 415 pregnant and 431 410 nonpregnant women 15 to 44 years of age with symptomatic COVID-19) | 3.0 (2.6, 3.4)                  | 2.9 (2.2, 3.8) | 24 (1.5, 40) | 1.7 (1.2, 24)     |
| Lokken 2021\(^\text{26}\)   | Analysis of data from 35 large hospitals and clinic systems in Washington State (240 pregnant women and 32 902 individuals 20 to 39 years of age with COVID-19) | 3.5 (2.5, 5.3)                |                |              |                   |      | 13.6 (2.7, 43.6) |
| Knobel 2021\(^\text{32}\)   | Analysis of data from a national surveillance system in Brazil (nonobstetric [\(n = 19\ 052\)], pregnant [\(n = 2114\)], and postpartum [\(n = 510\)] women 10 to 45 years of age) | Pregnant versus nonobstetric: 18.7% versus 24.4% | Pregnant versus nonobstetric: 7.4% versus 10.7% | Postpartum versus nonobstetric: 34.0% versus 24.4% | Postpartum versus nonobstetric: 20.9% versus 10.7% |      | Pregnant versus nonobstetric: OR (95% CI), .6 (.5, .7) |
| Queadan 2021\(^\text{5}\)   | Retrospective analysis of data from the Cerner COVID-19 de-identified cohort, which contains patient-level data extracted from electronic medical records of participating US hospitals (609 pregnant patients and 20 884 nonpregnant patients 18 to 44 years of age with COVID-19) | 60.5% versus 17.0%, \(P < .001\) | Moderate ventilation: 1.7% versus 7%, \(P < .001\); invasive ventilation: 1.6% versus 1.9%, \(P = .48\) |      | .2% versus .5%, \(P = .26\) |

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OR, odds ratio.
\(^a^\)Unless otherwise indicated.
\(^b^\)Statistically significant findings in boldface.
nausea and vomiting. Three community-based studies (one in Mexico, two in the United States) reported significantly greater hospitalization rates among pregnant versus nonpregnant women with COVID-19.\textsuperscript{5,26,31} Additionally, an analysis of US surveillance data from the Centers for Disease Control and Prevention (CDC) observed a higher risk of ICU admission in pregnant compared with nonpregnant women with COVID-19;\textsuperscript{4} although the Mexican study did not support this relationship.\textsuperscript{31} Two analyses of US surveillance data also reported increased mortality risk in pregnant versus nonpregnant patients with COVID-19,\textsuperscript{4,26} but this finding was not consistent across community-based studies.\textsuperscript{5,31} Interestingly, multiple logistic regression analysis of data from a Brazilian national surveillance system found that relative to nonobstetric COVID-19 cases (defined as flu-like symptoms in addition to dyspnea, respiratory distress, and/or oxygen saturation below 95%), mortality risk was elevated in postpartum cases (OR, 1.9; 95% CI, 1.5, 2.4) but decreased in pregnant cases (.6; .5, .7). The authors noted that the less frequent hospital admission of pregnant women with low oxygen saturation compared with postpartum/nonobstetric patients may have contributed to these results.

Several studies have evaluated risk factors for severe COVID-19 or ICU admission in pregnancy. In a meta-analysis, increasing maternal age, high body-mass index (BMI), pre-existing comorbidities, and pregnancy-specific disorders (e.g., gestational diabetes, preeclampsia) were associated with severe COVID-19; these factors in addition to non-White ethnicity were associated with increased risk for ICU admission.\textsuperscript{2} Non-White ethnicity and high BMI were associated with maternal death and a need for invasive ventilation. These findings are generally consistent with subsequently published reports.\textsuperscript{26,33–36} Additionally, a retrospective analysis of 473 902 hospitalized pregnant US women, 8584 with COVID-19, reported the highest relative risk of poor clinical outcomes, including maternal death, among Hispanic and Black non-Hispanic women.\textsuperscript{33}

### 2.3 Effect of COVID-19 on pregnancy outcomes

Antepartum SARS-CoV-2 infection is associated with substantial morbidity and mortality risk in parents and infants compared with uninfected pregnant women (Tables \ref{table1} and \ref{table2}).\textsuperscript{5,33,37–45} Although background maternal/fetal and infant adverse outcomes are generally much more common in LMIC,\textsuperscript{46} increased risks of these outcomes associated with COVID-19 occur in both high-income countries (HIC) and LMIC.\textsuperscript{5,8} A cohort study of 2130 pregnant women (n = 706 with COVID-19) at 43 institutions in 18 countries found that pregnant women with COVID-19 had substantially higher rates than uninfected women of severe maternal morbidity, neonatal complications, preeclampsia/eclampsia/low platelet count syndrome, ICU admission, infections requiring antibiotics, and preterm birth.\textsuperscript{5} Similarly, a meta-analysis found elevated rates of maternal all-cause mortality (OR, 2.9; 95% CI, 1.1, 7.5), ICU admission (18.6; 7.5, 45.8), preterm birth (1.5; 1.1, .9), neonatal ICU (NICU) admission (4.9; 1.9, 12.8), and stillbirth (2.8; 1.3, 6.5) among women with versus without COVID-19; differences in risk of Cesarean section (C-section) and neonatal death were not statistically significant.\textsuperscript{2} A meta-analysis of pregnancy outcomes from 17 countries during January 2020–January 2021 also reported significant increases in maternal and fetal mortality, but not neonatal death, associated with COVID-19; subgroup analyses indicated statistical significance in LMIC but not HIC.\textsuperscript{7} Similarly, a meta-analysis of data from 35 countries found that adverse pregnancy/neonatal COVID-19 outcomes were significantly more common in LMIC, likely due to limited access to healthcare, compared with HIC.\textsuperscript{8} In Brazil, data from the National Ministry of Health’s Epidemiological Surveillance Information System showed that the overall case fatality rate (CFR) for pregnant women admitted with severe acute respiratory syndrome due to COVID-19 was 6.3%. This rate was approximately ten times higher compared with that reported for the United States (.6%). Furthermore, when comparing CFR and mortality rates among White versus Black women in Brazil, a substantially higher burden and worse maternal outcomes were observed among Black women. Interestingly, these racial disparities were also observed in pregnant women in the United States, probably reflecting inequalities in access to quality health care.\textsuperscript{47}

The mechanisms underlying poor maternal and fetal outcomes associated with maternal SARS-CoV-2 infection are not fully understood.\textsuperscript{48} SARS-CoV-2 enters respiratory epithelial cells by attaching to angiotensin-converting enzyme 2 (ACE2), which is found in various parts of the body, via the spike protein.\textsuperscript{49,50} Age-dependent ACE2 expression may account for lower risk of COVID-19 among children relative to adults.\textsuperscript{59} In the placentas of women without COVID-19, ACE2 is highly expressed in the first and second trimesters but is virtually absent at term, suggesting that ACE2-mediated risk of placental infection may peak earlier during pregnancy.\textsuperscript{48} Furthermore, ACE2 expression in placental tissue collected at term was significantly higher in COVID-19 cases compared with noninfected women and in women with severe versus asymptomatic COVID-19.\textsuperscript{51} Accordingly, high placental ACE2 levels may reflect inflammatory placental changes, potentially contributing to poor pregnancy outcomes, even without viral placental infection.\textsuperscript{52}

Vertical transmission can occur through breast milk or during pregnancy; however, evidence suggests transmission is rare.\textsuperscript{53–57} With regard to breast milk, most studies have found no clinical evidence of vertical transmission or infection through breast milk to newborns from mothers with confirmed/suspected SARS-CoV-2 infection.\textsuperscript{53,55,56,57} In a retrospective cohort analysis, almost all of 101 newborns born to mothers with confirmed/suspected COVID-19 at a large New York City medical center tested negative for COVID-19 at 0–25 days of life, with the two indeterminate test results possibly indicating low viral load or lack of an actual infection; there was no evidence of clinical-based transmission.\textsuperscript{54} However, some evidence suggests that vertical transmission during pregnancy may occur in a limited number of cases.\textsuperscript{55} A meta-analysis revealed low rates (3.2%) of vertical transmission during the third trimester.\textsuperscript{55} In another study, among infants born to women with laboratory-confirmed COVID-19 in the Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET), 2.6% of infants for whom molecular tests were performed were perinatally infected, primarily those born to women with infection at delivery.\textsuperscript{58}
| Study                  | Country | No. pregnancies/No. with COVID-19 | Required supplemental oxygen, RR<sup>a,b</sup> (95% CI) | Required invasive mechanical ventilation or ECMO, RR<sup>a,b</sup> (95% CI) | Preeclampsia/eclampsia, RR<sup>a,b</sup> (95% CI) | Premature membrane rupture, RR<sup>a,b</sup> (95% CI) | ICU admission, RR<sup>a,b</sup> (95% CI) | C-section/ emergency C-section, RR<sup>a,b</sup> (95% CI) | Postpartum hemorrhage, RR<sup>a</sup> (95% CI) | Death, RR<sup>a</sup> (95% CI) |
|-----------------------|---------|----------------------------------|------------------------------------------|-------------------------------------------------|-----------------------------------------------|-----------------------------------|-------------------------------|---------------------------------|---------------------------------|----------------------|
| Villar 2021<sup>6</sup> | International<sup>c</sup> | 2130/706 | 1.8 (1.3, 2.4) | .9 (.7, 1.1) | 5.0 (3.1, 8.1) | 1.3 (1.2, 2.4) | 22.3 (2.9, 172.1) |
| **High-income countries** | | | | | | | | | | |
| Ackerman<sup>33</sup> | USA | 473 902/8584 | Pregnant: 2.7 (2.5, 3.0) | Delivered: 1.6 (1.4, 1.8) | Pregnant: 11.9 (10.2, 13.9) | Delivered: 12.0 (9.8, 14.8) | Pregnant: 7.6 (6.9, 8.5) | Delivered: 7.0 (6.1, 8.1) | Pregnant: 13.3 (7.3, 24.4) | Delivered: 23.6 (11.8, 55.6) |
| Chinn 2021<sup>37</sup> | USA | 869 079/18 715 | | | 14.3 (12.5, 16.4) | OR, 5.8 (5.5, 6.3) | OR, 15.4 (9.7, 24.4) |
| Ko 2021<sup>38</sup> | USA | 489 471/6550 | aRR, 12.7 (9.2, 17.5) | | | aRR, 3.6 (2.8, 4.5) | | aRR, 17.0 (8.2, 35.4) |
| Gurol-Uganci 2021<sup>39</sup> | UK | 342 080/3527 | aOR, 1.6 (1.3, 1.9) | | | aOR, 1.6 (1.5, 1.8) | | |
| Crovetto 2021<sup>40</sup> | Spain | 2225/317 | | | | | | | |
| Martinez-Perez 2021<sup>41</sup> | Spain | 1009/246 | | | | | | | |
| Ahlberg 2020<sup>42</sup> | Sweden | 759/155 | aPR, 1.84 (1.00, 3.36) | | | | | | |
| **Low- and middle-income countries** | | | | | | | | | | |
| Cardona-Perez 2021<sup>43</sup> | Mexico | 240/70 | aOR, 2.1 (8.5, 2) | aOR, 1.1 (5, 3.1) | EE, 1.14 (−.25, 5.7) | EE, 28.5 (18.9, 37.4) | EE, .68 (−.1, 4.7) |
| Gupta 2021<sup>44</sup> | India | 3165/108 | | | | | | | |
| Hcini 2021<sup>45</sup> | French Guiana | 507/137 | 4.5 (1.1, 18.6) | | | | | | |

Abbreviations: aOR, adjusted odds ratio; aPR, adjusted prevalence ratio; aRR, adjusted relative risk; CI, confidence interval; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; EE, estimated effect; ICU, intensive care unit; OR, odds ratio; RR, relative risk.

<sup>a</sup>Unless otherwise indicated.

<sup>b</sup>Statistically significant findings in boldface.

<sup>c</sup>Includes Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, UK, and US.
TABLE 3 Fetal/infant pregnancy outcomes for women with and without COVID-19

| Study                        | Country            | No. pregnancies/No. with COVID-19 | Preterm, RR<sup>a,b</sup> (95% CI) | NICU admission, RR<sup>a,b</sup> (95% CI) | Stillbirth/intrauterine fetal death, RR<sup>a,b</sup> (95% CI) | Low birth weight, RR<sup>a,b</sup> (95% CI) | Neonatal death, RR<sup>a,b</sup> (95% CI) |
|------------------------------|--------------------|----------------------------------|------------------------------------|------------------------------------------|------------------------------------------------|------------------------------------------|------------------------------------------|
| Villar 2021<sup>6</sup>      | International<sup>f</sup> | 2130/706                         | 1.6 (1.3, 1.9)                     |                                          |                                              |                                          |                                          |
| **High-income countries**    |                    |                                  |                                    |                                          |                                              |                                          |                                          |
| Ackerman (submitted)<sup>33</sup> | USA                | 473 902/8584                     | 1.3 (1.2, 1.5)                     | 1.4 (1.1, 1.7)                           | 1.2 (1.0, 1.6)                               | 2.2 (1.6, 3.1)                           | 4.2% (−0.3%, 9.9%)                       |
| Ko 2021<sup>38</sup>         | USA                | 489 471/6550                     | aRR, 1.2 (1.1, 1.3)                | aRR, 1.2 (1.0, 1.6)                      |                                               |                                          |                                          |
| Gurol-Uganci 2021<sup>39</sup> | UK                 | 342 080/3527                     | aOR, 2.2 (2.0, 2.4)                | aOR, 2.2 (1.6, 3.1)                      |                                               |                                          |                                          |
| Crovetto 2021<sup>40</sup>   | Spain              | 2225/317                         | Risk difference, 4.2% (−3%, 9.9%) | Risk difference, 8% (−2.3%, 5.5%)       | Perinatal death: risk difference, 1% (−7%, 2.7%) |                                          |                                          |
| Martinez-Perez 2021<sup>41</sup> | Spain              | 1009/246                         | aOR, 2.1 (1.3, 3.4)                | aOR, 4.6 (2.4, 8.9)                      |                                               |                                          | .6% versus .7% (no ratio estimated)     |
| Ahlberg 2020<sup>42</sup>    | Sweden             | 759/155                          |                                     |                                          |                                               |                                          |                                          |
| **Low- and middle-income countries** |                    |                                  |                                    |                                          |                                              |                                          |                                          |
| Cardona-Perez 2021<sup>43</sup> | Mexico             | 240/70                           | aOR, 1.2 (2, 6.6)                  |                                          |                                              |                                          |                                          |
| Gupta 2021<sup>44</sup>     | India              | 3165/108                         | EE, 13.7 (5.9, 22.9)               | EE, 4.6 (−5, 12.2)                       | EE, 240 (152.4, 327.5)                        | EE, .6 (8.5, 2.2)                        |                                          |
| Hcini 2021<sup>45</sup>     | French Guiana      | 507/137                          | 4.7 (14, 15.9)                     |                                          |                                              |                                          |                                          |

aOR, adjusted odds ratio; aRR, adjusted relative risk; CI, confidence interval; COVID-19, coronavirus disease 2019; EE, estimated effect; NICU, neonatal intensive care unit; RR, relative risk.

<sup>a</sup>Unless otherwise indicated.

<sup>b</sup>Statistically significant findings in boldface.

<sup>f</sup>Includes Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, UK, and US.
2.4 Immune responses to SARS-CoV-2 in pregnant women

SARS-CoV-2 infection in pregnancy is associated with placental inflammation and reduced antiviral antibody responses. In one study, pregnant women with COVID-19 (*n* = 22) had reduced levels of immunoglobulin (Ig) G antibodies against the receptor-binding domain of the spike protein (S-RBD-IgG) and were less likely to have detectable neutralizing antibodies (nAb) compared with nonpregnant infected women (*n* = 17). Relative to umbilical cord serum, maternal serum featured significantly greater nAb titers but similar antispike and anti–S-RBD IgG titers, suggesting that SARS-CoV-2 infection does not broadly affect maternal transfer of humoral immunity. As noted previously, SARS-CoV-2 may induce a specific maternal inflammatory response without viral transfer to the placenta. In a study of 23 pregnant women, those with SARS-CoV-2 infection had higher serum IgG/IgM levels compared with uninfected women; infection was also associated with placental inflammatory responses characterized by T cells and macrophages. A cytokine response was observed in umbilical cord blood, possibly indicating fetal inflammation, but did not compromise cellular immunity. Furthermore, SARS-CoV-2 was not detected in placental tissues.

2.5 Transfer of immunity against SARS-CoV-2

2.5.1 Maternal-fetal

Several studies suggest transplacental transfer of maternal IgG antibodies to SARS-CoV-2; however, it is yet unknown whether the quantity and quality of these antibodies will sufficiently protect infants in early life. Among 83 infants born at a single US hospital to pregnant women seropositive for SARS-CoV-2 during pregnancy, 72 (87%) were seropositive. IgG, but not IgM, antibodies were detected in cord blood of seropositive infants, and maternal SARS-CoV-2 IgG concentrations were positively correlated with umbilical cord IgG concentrations. Higher IgG/IgM concentrations in mothers were observed with moderate/critical versus asymptomatic/mild SARS-CoV-2 infection, and infants born to women with moderate/critical versus asymptomatic SARS-CoV-2 infection generally had higher IgG concentrations (nonsignificant).

2.6 Transfer of antibodies in breast milk

In addition to maternal-fetal antibody transfer, SARS-CoV-2–reactive antibodies in breast milk may bolster passive immunity in infants. Levels of antibodies to the SARS-CoV-2 spike and nucleocapsid proteins were significantly higher in human milk collected during versus before the COVID-19 pandemic. Furthermore, breast milk from women previously infected with SARS-CoV-2 had higher anti–RBD-reactive IgA/IgG concentrations compared with prepandemic negative-control samples. In one study, 21/34 (62%) breast milk samples from women with previous COVID-19 infection effectively neutralized SARS-CoV-2 infectivity in vitro, supporting recommendations encouraging breastfeeding in women with previous mild to moderate COVID-19.

2.7 COVID-19 vaccination in pregnancy

2.7.1 Vaccine safety

Large-scale vaccine safety data are emerging from surveillance during national vaccination programs. For the US mass vaccination program, safety findings were reported from multiple databases. The v-safe surveillance system included 35,961 pregnant women who received either the BNT162b2 messenger ribonucleic acid (mRNA; Pfizer–BioNTech) or the mRNA-1273 (Moderna) vaccine through February 28, 2021. Injection site reactions were similarly frequent among pregnant and nonpregnant women, with slight variations in reporting patterns of specific local and systemic reactions. In the v-safe pregnancy registry, spontaneous abortion incidence among 2456 vaccinated women through July 19, 2021, was consistent with prepandemic estimates; a separate analysis found similar results for neonatal outcomes among 1634 infants. Among 221 Vaccine Adverse Event Reporting System (VAERS) reports involving pregnant women who received a COVID-19 vaccine through February 28, 2021, 66 (29.9%) concerned pregnancy- or neonatal-specific adverse events, most commonly spontaneous abortion (*n* = 46; 37 in the first trimester). No congenital anomalies were reported. An analysis of data from the Vaccine Safety Datalink through June 28, 2021, indicated that among 105,446 unique pregnancies, spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination compared with ongoing pregnancies; similar results were observed for rates of stillbirth with antepartum COVID-19 vaccine exposure.

An online prospective cohort study found that among women who were pregnant (*n* = 7809), lactating (*n* = 6815), or planning to become pregnant (*n* = 2901), the most common adverse reactions to COVID-19 vaccination (mostly with mRNA vaccines) were injection site pain and fatigue. Frequencies of adverse reactions were higher after the second dose than the first dose and were generally similar or lower among pregnant women compared with women who were neither pregnant nor lactating. No severe maternal/infant adverse effects were reported in a prospective assessment of lactating women who received...
BNT162b2 (n = 27) or mRNA-1273 (n = 21).76 Adverse reactions were reported significantly more frequently after the first and second mRNA-1273 doses (100% for both) compared with BNT162b2 (78% for both; P = .02 for both comparisons); all resolved ≤ 72 h postvaccination. Additionally, maternal COVID-19 vaccination was not associated with an increase in polyethylene glycol (PEG)-ylated proteins, or, as the same authors demonstrated separately, detection of COVID-19 vaccine mRNA, in human milk.76,77

A retrospective cohort study found no significant differences in rates of adverse perinatal/pregnancy outcomes, including preterm birth, stillbirth, fetal abnormalities, intrapartum pyrexia, postpartum hemorrhage, C-section, maternal ICU/NICU admission, or infant small for gestational age between COVID-19–vaccinated (n = 133; ≥ 1 dose) and propensity-matched unvaccinated (n = 399) women who delivered between March 1, 2021, and July 4, 2021, at a UK academic hospital.78 Similarly, analysis of a vaccine registry linked to the Mayo Clinic Health System delivery registry found similar rates of adverse maternal/neonatal outcomes among vaccinated (≥ 1 dose) and unvaccinated patients.79

Rare cases of thrombotic events and thrombocytopenia, predominantly among young women with unspecified pregnancy status, have been reported after vaccination with the recombinant nonreplicating adenoviral vector vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Janssen/Johnson & Johnson).80,81 In Brazil, use of ChAdOx1 nCoV-19 was suspended in May 2021 after a 35-year-old pregnant woman died from a hemorrhagic stroke after vaccination.82

2.8 Immunogenicity

A prospective cohort study observed equivalent antibody titers induced by BNT162b2 and mRNA-1273 vaccination in pregnant/lactating and nonpregnant women.53 Notably, postvaccination titers across groups were significantly higher than those following antepartum SARS-CoV-2 infection (P < .001).

2.9 Real-world vaccine effectiveness

A retrospective cohort study conducted within a large Israeli pregnancy registry identified 10 and 46 infections among BNT162b2-vaccinated (n = 7530) and matched unvaccinated (n = 7530) pregnant women, respectively, occurring ≥ 28 days postdose 1; corresponding hazards of infection were 0.22 (95% CI, 0.11, 0.43, P < .001).84 Additionally, the aforementioned Mayo Clinic Health System analysis found that patients fully vaccinated during pregnancy were significantly less likely than unvaccinated pregnant patients to become infected with SARS-CoV-2 before delivery (2/140 [1.4%] vs 210/1861 [11.3%], P < .001); the two infections in vaccinated patients occurred before vaccination.79 An Israeli observational cohort study including SARS-CoV-2–naive pregnant women found that BNT162b2 vaccine effectiveness 7–56 days postdose 2 was 96% (95% CI, 89%, 100%) for any infection, 97% (91%, 100%) for symptomatic infection, and 89% (43%, 100%) for COVID-19–related hospitalization.85

2.10 Maternal-fetal transfer of immunity following vaccination

Analysis of maternal and fetal (cord blood) samples indicates IgG antibody transfer to fetuses following COVID-19 mRNA vaccination of pregnant women.67,86,87 An Israeli multicenter study identified robust humoral IgG responses in maternal and cord blood collected at delivery among women who received BNT162b2 (n = 86) or with confirmed SARS-CoV-2 infection (n = 65) during pregnancy.67 The maternal humoral IgG response to vaccination crossed the placental barrier to the fetal circulation ≤ 15 days postdose 1. The overall maternal-to-neonatal IgG transfer ratio was similar for immunization and natural infection but generally lower for infections in late gestation, possibly indicative of lagging transplacental antibody transfer. In a real-world study of hospitalized children < 6 months of age (with COVID-19, n = 176; without COVID-19, n = 203), the effectiveness of maternal vaccination with a two-dose primary mRNA COVID-19 series against hospitalization was 61% (95% CI, 31%, 78%). Effectiveness was highest when the vaccination series was completed later in pregnancy (21 weeks through 2 weeks before delivery; efficacy, 80% [95% CI, 55%, 91%]).88

The disappearance of the cytotrophoblast layer between syncytiotrophoblasts and stromal cells, which occurs after the fourth month until the end of gestation, exposes the syncytiotrophoblast cells to maternal blood vessels and increases the expression of the FcRn receptor in the placenta, allowing active transfer of IgG. This phenomenon suggests that vaccination in the early stages of gestation is not likely to induce an efficient transfer of antibodies.89

2.11 Transfer of antibodies in breast milk following vaccination

Administration of BNT162b2 and mRNA-1273 in lactating women results in robust secretion of SARS-CoV-2 antibodies in breast milk.83,90-93 In the aforementioned prospective cohort study, breast milk from lactating women administered mRNA vaccines contained SARS-CoV-2 antibodies, with IgG levels increasing postdose 2.83 Similarly, a prospective study demonstrated a rapid increase in anti–SARS-CoV-2 IgA antibodies in breast milk from lactating women following BNT162b2 vaccination (n = 84); IgA/IgG levels further increased postdose 2.91 Antibodies in breast milk showed neutralizing activity, indicating potential passive immunity against newborn infection. A Brazilian study in lactating women given two doses of an inactivated virus vaccine (Coronavac; Sinovac Biotech Ltd–Instituto Butantan) found detectable anti–SARS-CoV-2 IgA antibodies, above seroconversion levels, in breast milk that persisted up to 4 months postdose 1 in 50% of participants.94
FIGURE 1  Summary of findings on COVID-19 impact and immunity in pregnant and lactating women.\textsuperscript{2,4,6,10–12,53–58,64–68,70–74,83,86,87,90–93,97,104,111–114,116} The dashed “X” is intended to indicate that transfer of antibodies (or lack thereof) after natural infection is not well established. ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; ICU, intensive care unit; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; JCVI, Joint Committee on Vaccination and Immunisation; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMFM, Society for Maternal-Fetal Medicine

3 | DISCUSSION

The COVID-19 pandemic has profoundly affected pregnant women worldwide, particularly in LMIC. Data overwhelmingly suggest that pregnant versus nonpregnant women with COVID-19 more frequently require hospitalization, ICU admission, and invasive ventilation\textsuperscript{2,5,26,31} compared with uninfected pregnant women. COVID-19 is also associated with increased risk of poor maternal/neonatal outcomes, including preeclampsia, preterm birth, maternal/infant ICU admission, invasive ventilation, maternal death, and stillbirth (Figure 1).\textsuperscript{2,6,37} In Brazil, pregnant women with COVID-19 have consistently experienced high mortality rates since the pandemic’s early phase.\textsuperscript{14,16} Notably, pregnant women remain at risk compared with the general population regardless of the variant.\textsuperscript{23} Furthermore, meta-analyses indicate particular vulnerability of LMIC to COVID-19–related adverse pregnancy/neonatal outcomes, likely reflecting healthcare access disparities.\textsuperscript{7,8} COVID-19 vaccine acceptance is generally higher in LMIC compared with HIC. A large study, including 44,260 individuals, analyzed COVID-19 vaccine acceptance in 10 LMICs ($n = 20,176$) in Asia, Africa, and South America and from Russia (upper-middle income) and the United States (HIC; $n = 24,084$). Personal protection against COVID-19 was the main reason for vaccine acceptance among LMIC respondents, and concern about side effects was the most common reason for vaccine hesitancy.\textsuperscript{95} Health workers were considered the most trusted sources of information about COVID-19 vaccines. However, we have to acknowledge that LMICs face considerable challenges in both receiving and distributing vaccine doses.\textsuperscript{96}

Although most studies found no evidence of vertical SARS-CoV-2 transmission through breast milk to newborns from infected mothers, evidence exists that it may occur in a small proportion of cases (Figure 1).\textsuperscript{53–58,97} In contrast, there is clear evidence of antibody transfer via the placenta and breast milk of infected and convalescent women.\textsuperscript{57,64–69} COVID-19 vaccination may protect pregnant women\textsuperscript{79,84,85} and may secondarily benefit offspring, both by preventing adverse fetal outcomes associated with maternal COVID-19\textsuperscript{2,6–8} and via antibody transfer.\textsuperscript{67} Real-world immunogenicity and effectiveness studies demonstrate that mRNA antepartum COVID-19 vaccination elicits robust immune responses\textsuperscript{83} and reduces the risk of SARS-CoV-2 infection, symptomatic infection, and hospitalization.\textsuperscript{79,84,85} mRNA vaccination of pregnant and lactating women results in IgG transfer via the placenta and breast milk, respectively, thus protectively benefiting newborns (Figure 1).\textsuperscript{57,83,86,87,90–93} mRNA vaccine safety profiles are similar in pregnant and nonpregnant women, with no observed adverse effects on pregnancy outcomes.\textsuperscript{70,71,75,78} Additionally, maternal vaccination may reduce hospitalization due to COVID-19 among newborns.\textsuperscript{88} In the real-world study conducted in the United
TABLE 4  Recommendations by public health organizations on breastfeeding in women with COVID-19 and vaccination while pregnant or breastfeeding

| Organization                                      | Breastfeeding women with COVID-19                                                                 | Women who are pregnant or considering pregnancy                                                                 | Breastfeeding women                                                                                     |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| World Health Organization (WHO) 
(100,105-107,109,110)                            | Mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue breastfeeding | - Pregnant women should be vaccinated only when the benefits outweigh the potential risks  
- Pregnant individuals are free to select Pfizer–BioNTech, Moderna, AstraZeneca, Janssen, Sinopharm (BIBP, inactivated), or Sinovac (Coronavac, inactivated) COVID-19 vaccines | Lactating women should be offered COVID-19 vaccination  
Lactating individuals are free to select Pfizer–BioNTech, Moderna, AstraZeneca, Janssen, Sinopharm (BIBP, inactivated), or Sinovac (Coronavac, inactivated) COVID-19 vaccines  
WHO does not recommend discontinuing breastfeeding after vaccination |
| Centers for Disease Control and Prevention (CDC) 
(101,103)                                        | Women with COVID-19 should wash hands before and wear a mask during breastfeeding  
Women should discuss risks and benefits, including ease of breastfeeding and rooming in with their newborns, with their healthcare providers | Vaccination is recommended for pregnant women or women who may become pregnant in the future  
Pregnant individuals and those trying to become pregnant are free to select Pfizer–BioNTech, Moderna, or Janssen COVID-19 vaccines but should be informed of the risk of thrombocytopenia syndrome after receipt of Janssen (Johnson & Johnson) COVID-19 vaccine and the availability of other options | Vaccination is recommended for lactating women  
Pregnant individuals are free to select Pfizer–BioNTech, Moderna, or Janssen COVID-19 vaccines but should be informed of the risk of thrombocytopenia syndrome after receipt of Janssen (Johnson & Johnson) COVID-19 vaccine and the availability of other options |
| American College of Obstetricians and Gynecologists (ACOG) 
(10)                                            | All eligible persons, including pregnant individuals and those actively trying to become pregnant or contemplating pregnancy, should receive a COVID-19 vaccine or vaccine series  
Pregnant individuals are free to select Pfizer–BioNTech, Moderna, or Janssen COVID-19 vaccines | All eligible persons, including lactating individuals, should receive a COVID-19 vaccine or vaccine series  
Lactating individuals are free to select Pfizer–BioNTech, Moderna, or Janssen COVID-19 vaccines  
There is no need to avoid initiation or discontinue breastfeeding in patients who receive a COVID-19 vaccine | Lactating women who are otherwise eligible should be offered the COVID-19 vaccine |
| Society for Maternal-Fetal Medicine 
(104)                                              | Pregnant women should have access to COVID-19 vaccines  
Pregnant women should discuss potential risks and benefits and engage in shared decision-making with clinicians regarding receipt of vaccine  
Healthcare professionals should counsel patients that the theoretical risk of fetal harm from mRNA vaccines is very low |  |  |
| Joint Committee on Vaccination and Immunisation (JCVI)/UK Health Security Agency 
(12,99)                                           | Benefits of breastfeeding outweigh potential risks of transmission | Women who are pregnant should be offered vaccination at the same time as nonpregnant women, based on their age and clinical risk group  
Pfizer–BioNTech and Moderna vaccines are the preferred vaccines to offer to pregnant women  
Women who become pregnant after starting a vaccine course should complete vaccination during pregnancy using the same vaccine product, unless contraindicated | Breastfeeding women may be offered any suitable COVID-19 vaccine |

COVID-19, coronavirus disease 2019.
States during Delta and Omicron circulation, maternal vaccination reduced the risk for COVID-19 hospitalization among infants aged < 6 months.

Various organizations have issued guidance to address the unique burden affecting not only pregnant women but also recently pregnant and lactating women. In a recent study performed in Brazil, rates of death were higher among postpartum women with COVID-19 compared with pregnant women with COVID-19.47 In a retrospective cohort study in the United States that included 14,104 patients, SARS-CoV-2 infection was associated with increased risk of a composite outcome of maternal mortality or serious morbidity from obstetric complications in pregnant as well as postpartum individuals.98 Considering the relative rarity of serious COVID-19 in infants, the limited reports of vertical SARS-CoV-2 transmission, and protective benefits of breastfeeding, the WHO and the UK Health Security Agency12 encourage breastfeeding among mothers with COVID-19 (Table 4).99,100 The CDC does not provide a clear corresponding recommendation but does provide hygiene guidance (i.e., handwashing and mask-wearing) for those choosing to breastfeed and encourages related discussion with healthcare providers regarding rooming in with newborns.101

Public health organizations generally recommend vaccination of pregnant/lactating women (Table 4). Although other organizations provide stronger recommendations,10,12,102–104 the WHO recommends antepartum vaccination when benefits outweigh potential risks (e.g., high risk of COVID-19 exposure, comorbidities associated with high risk for severe COVID-19) but recommends vaccination of lactating women as for other adults.105–110 The CDC recommends that women who are pregnant, trying to become pregnant, or lactating be informed of the risk of thrombocytopenia syndrome after receipt of Ad26.COV2.S and the availability of other options.103

Current knowledge regarding long-term COVID-19 vaccine safety and effectiveness among pregnant/lactating women is limited to observational data. The first vaccine trial in pregnant women (NCT04754594) is a phase 2/3, randomized, placebo-controlled, observer-blinded study evaluating safety, tolerability, and immunogenicity of BNT162b2 in healthy pregnant participants (n = ~700); enrollment began in February 2021 and study completion is projected in October 2022.111 Also currently recruiting is a phase 2, randomized, open-label study of Ad26.COV2.S in healthy pregnant patients (n = ~700; NCT04765384; HORIZON1); projected primary completion and study completion dates are January 2023 and September 2024, respectively.112 Additional studies include an observational outcomes study of mRNA-1273 in pregnancy (NCT04958304).113 A UK study (Preg-CoV) evaluating different dosing intervals of BNT162b2 and mRNA-1273 in pregnant women,114 and a WHO-led study assessing outcomes of pregnant/recently pregnant women infected with SARS-CoV-2.115

Future investigations are warranted to evaluate the clinical efficacy of COVID-19 vaccination during pregnancy/lactation; the safety, immunogenicity, and efficacy of COVID-19 vaccines administered concomitantly with other vaccines (e.g., influenza) in the general population and in pregnant/lactating women; and the impact of emerging SARS-CoV-2 variants on pregnancy outcomes and vaccine efficacy against resulting disease in pregnant/lactating women. Vaccine hesitancy and access issues among pregnant/lactating women must be urgently addressed, especially in low-income regions. Successful implementation of COVID-19 vaccination strategies will likely substantially reduce SARS-CoV-2–associated morbidity and mortality in these vulnerable populations.

ACKNOWLEDGEMENTS
Editorial/medical writing support was provided by Sheena Hunt, PhD, and Adrienne Drinkwater, PhD, of ICON (Blue Bell, PA) and was funded by Pfizer Inc.

CONFLICTS OF INTEREST
Marco A. P. Safadi has received research grants and consultancy fees from Pfizer, GlaxoSmithKline, AstraZeneca, Janssen, and Sanofi-Pasteur. Julia Spinardi and Amit Srivastava are employees of Pfizer Inc and may hold stock or stock options. David Swerdlow was an employee of Pfizer at the time of manuscript preparation and holds stock and stock options.

DATA AVAILABILITY STATEMENT
Data are available from the cited references.

ORCID
Amit Srivastava https://orcid.org/0000-0002-2510-5058

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Safadi MAP, Spinardi J, Swerdlow D, Srivastava A. COVID-19 disease and vaccination in pregnant and lactating women. Am J Reprod Immunol. 2022;88:e13550. https://doi.org/10.1111/aji.13550