COVID-19 and novel mRNA vaccines in pregnancy: an updated literature review

E Joubert, AC Kekeh, CN Amin

*Campbell University School of Osteopathic Medicine, Lillington, NC, USA  b Edward Via College of Osteopathic Medicine-Virginia Campus, Blacksburg, VA, USA  c Piedmont Family Medicine, Salisbury, NC, USA

Correspondence: E Joubert, Campbell University Jerry M Wallace School of Osteopathic Medicine, 4350 US-421, Lillington, NC 27546, USA.

Email: eloisejoubert93@gmail.com

Accepted 5 October 2021. Published Online 1 November 2021.

The novel coronavirus, SARS-CoV-2, or COVID-19, has affected the world on a pandemic scale resulting in catastrophic outcomes and deaths. Currently, there is limited safety data specific to mRNA vaccine use in pregnant or lactating individuals and the potential risks to a pregnant individual and the fetus are unknown. We report an updated literature review of current information and evidence available to aid in the decision whether to vaccinate against COVID-19 currently being made by pregnant individuals and their healthcare providers so that they are able to make a well-informed recommendation and decision.

Keywords: Clinical guidelines, epidemiology: infectious diseases, health services research, infectious disease: virology, risk management.

Introduction

The unexpected and extraordinary year of 2020 will forever be remembered due to the profound impacts of SARS-CoV-2 and the collaborative scientific achievements made for the betterment of global health. The novel coronavirus has continued to affect the world on a pandemic scale, resulting in catastrophic outcomes and deaths. More than 228 million confirmed cases and 4.6 million deaths have been attributed to COVID-19 globally.¹ This created an urgency for more innovative techniques and vaccine research that led to the development of mRNA vaccines. As vaccine development has rapidly grown more complex and sophisticated over the years, it is important to acknowledge the risks and benefits when recommending new vaccines, especially to special populations: specifically, pregnant individuals. The literature review was conducted primarily using PubMed and Google Scholar databases with a focus on the Pfizer-BioNtech and Moderna vaccines. Search terms included combinations of coronavirus, COVID-19 and lactation, mRNA vaccines in pregnancy, SARS-CoV-2 and pregnancy, messenger RNA, Moderna, Pfizer.

Novel mRNA vaccines

The SARS-CoV-2 genome was sequenced in January 2020 and kickstarted the development of the novel vaccine against the SARS-CoV-2 virus. Unlike other formulations of vaccines, researchers relied on decades of previous research and biotechnology to develop an mRNA vaccine, comprised of instructions on how to make the protein components unique to the COVID-19 virus. These vaccines consist of messenger RNA encapsulated by a lipid nanoparticle for delivery into the host cells. The mechanism of the mRNA vaccine after bolus injection into the subcutaneous space and endocytosis into host cells is displayed well by Chaudhary et al. in Figure 1.² The mRNA within COVID-19 vaccine is taken up by dendritic cells. Ribosomes interpret the vaccine’s mRNA to generate the coronavirus spike protein that is presented on the surface of dendritic cells. The host’s immune system recognises these spike proteins and generates neutralising antibodies as a result, now supplied with the ability to develop a robust immunity upon recognition of the unique protein if infection by COVID-19 were to occur.³ Messenger RNA vaccines are not live virus vaccines and do not use an adjuvant to enhance efficacy. They do not enter the nucleus or alter human DNA in vaccine recipients and thus cannot cause any genetic changes.⁴ The U.S. Food and Drug Administration initially issued an emergency use authorisation (EUA) in December 2020 for both the Pfizer-BioNtech mRNA vaccine (BNT162b2) and Moderna mRNA-1273 vaccine. Although, the Pfizer vaccine is now approved by the FDA as of August 2021 for
use in individuals 16 years and older as a 2-dose regimen
given 21 days apart. Pfizer continues to be available under
EUA for individuals 12 through 15 years of age as of May
2021 and for administration of a third dose in certain
immunocompromised individuals. Moderna vaccine is also
available under EUA for use in individuals 18 years and
older as a 2-dose regimen given 28 days apart. As of
September 2021 in addition to the USA, Pfizer is also
approved for use in Bahrain, Brazil, Canada, New Zealand,
Saudi Arabia and Switzerland with EUA in many other
countries as well. Moderna is also approved for use in Canada
and Switzerland with EUA in many other countries.

Based on the unprecedented nature of the SARS-CoV-2
and the race to mitigate the effects of the virus on public
health, other alternative vaccines are also being studied
including viral vector vaccines, AstraZeneca and Janssen/
Johnson & Johnson, and a protein subunit vaccine, Nova-
vax. The World Health Organization retains a COVID-19
vaccine tracker that compiles data of each vaccine candi-
date and monitors their progression from pre-clinical
through Phase 3. The inactivated vaccine CoronaVac under
development by Sinovac Biotech in China, is created
through a process of chemical inactivation of SARS-CoV-2
without destruction to the integrity of its epitope structure
on surface antigens. Although this type of vaccine is
safer than live attenuated, it results only in a humoral
response and often requires booster doses to create long-
term immunity. A live attenuated vaccine, such as that
being developed in collaboration between Codagenix and
the Serum Institute of India, is generated through a process
by which SARS-CoV-2 virus is weakened so that it loses its
pathogenicity, but maintains capacity for growth within the
host. Several other vaccine platforms are summarised in
Figure 2 by Creech et al.

Based on the demonstrated efficacy in the phase II and
III clinical trials, it is expected that the safety and efficacy
profile of the vaccine for pregnant individuals would be
similar to the observed non-pregnant individuals included
in the studies by Pfizer and Moderna. Currently, there are
no safety data specific to mRNA vaccine use in pregnant or
lactating individuals and the potential risks to a pregnant
individual and the fetus are unknown. Both the emergency
use fact sheets for the Pfizer and Moderna vaccines state
that 'If you are pregnant or breastfeeding, discuss your
options with your healthcare provider', but have insuffi-
cient data to inform vaccine-associated risks. There is

Figure 1. Mechanism of mRNA vaccine after bolus injection into the subcutaneous space and endocytosis into host cells.
currently no concrete outlook for when pregnant women will be included in the vaccine recommendation guidelines. The pregnant population has historically been excluded from clinical trials for several reasons, including ethical concerns about fetal exposure, actual and perceived regulatory barriers, and liability concerns.

COVID-19 infection in pregnancy

Present data report that pregnant women who contract COVID-19 and become symptomatic are at an increased risk of pregnancy complications and mortality. In addition, Hispanic and non-Hispanic black pregnant women appear to be disproportionately affected by SARS-CoV-2 infection during pregnancy. According to the CDC COVID-19 data tracker, the majority of pregnant women infected with COVID-19 are 25–29 years old with 30–34 age group second and the 20–24, 35–39, 15–19, 40–44, 45–49, 50–54, 15 or less age groups following in the order greatest to least cases. The majority of the pregnant women were of white and Hispanic race. Of 97,521 of the cases in pregnant women in the USA where data were available during from 22 January 2020 to 20 September 2021, 21,823 were hospitalised. Of the data that were available, 534 of 15,780 were admitted to the ICU, 116 of 10,943 required invasive ventilation, and 25 of 11,403 required ECMO. Alloety et al. reported a spontaneous preterm birth rate of 6% in women with COVID-19. The odds of any preterm birth were higher in pregnant women with COVID-19 compared with those without the disease. A quarter of all neonates born to mothers with COVID-19 were admitted to the neonatal ICU, revealing an increased risk of admission compared with those born to mothers without COVID-19. The overall rate of caesarean section in COVID-19 infected mothers is also higher, ranging from 67.2% to 94%, and vaginal delivery from 6% to 32.8% of cases. The majority of these women were in their third trimester when the infection occurred. These data largely show that the pregnant population is not exempt from the detrimental impacts of COVID-19 and thus, along with the rest of the population, should seriously consider the benefits and risks of obtaining the novel vaccine.

Mechanism for increased risk

Current published data suggests that symptomatic pregnant patients with COVID-19 are at increased risk of more severe illness compared with nonpregnant patients, especially those with comorbidities such as hypertension, diabetes or cholestasis of pregnancy. The physiological, metabolic and vascular changes in normal and high-risk pregnancies may exacerbate these risks. In addition, the normal upregulation of angiotensin-converting enzyme 2 (ACE2) receptor during pregnancy was reported to play a major role. The...
upregulation of ACE2 receptor allows SARS-CoV-2 to bind and enter the host’s cells, thereby increasing the risk of infection during pregnancy. SARS-CoV-2, once bound to the ACE2 receptor, downregulates the expression of ACE2 receptor which leads to increased risk of vascular, endothelial cell and microcirculatory dysfunction including vascular constriction. This can further increase risk of miscarriages, premature births and intrauterine growth restrictions.

Zauche et al. studied patients enrolled in the v-safe pregnancy registry who had at least one dose of an mRNA COVID-19 vaccine preconception or prior to 20 weeks’ gestation and who did not report a pregnancy loss before six completed weeks’ gestation to assess the cumulative risk of spontaneous abortion (SAB). Among 2456 pregnant persons who received an mRNA COVID-19 vaccine preconception or prior to 20 weeks’ gestation, the cumulative risk of SAB from 6 to 19 weeks’ gestation was 14.1%. When compared with the expected range of SABs in recognised pregnancies, these data suggest that receiving an mRNA COVID-19 vaccine preconception or during pregnancy is not associated with an increased risk of SAB.

The virus can also exacerbate the hypercoagulable state of pregnancy leading to increased risks of DVTs, pulmonary embolism and stroke, which have been documented in cases of severe COVID-19-related illnesses. The increased susceptibility of COVID-19 infected and symptomatic pregnant women, as a result, has been associated with hospitalisation and increased risk for ICU admission and need for mechanical ventilation. In the study by Jering et al. on outcomes of hospitalised women giving birth with and without COVID-19, it was found that rates of mortality, myocardial infarction, venous thromboembolism, pre-eclampsia and preterm birth were higher in the women with COVID-19 who gave birth than those without COVID-19. The use of chest imaging, intensive care treatment and mechanical ventilation was also higher among the women who gave birth with COVID-19.

A systematic multi-national review of 60 studies on SARS-CoV-2 in pregnancy published in August 2020, found that severe illness occurred in up to 18% of pregnant patients and critical disease complicated up to 5% of cases, comparable to rates in the general population. This study also found that where universal testing was available, asymptomatic infection occurred in 43.5–92% of cases.

Safety data and current recommendation

Moderna studied their mRNA-1273 in rats during a combined developmental and perinatal/postnatal reproductive toxicity study that concluded that mRNA-1273 given before mating and during gestation periods at a dose of 100 microg did not have any adverse effects on female reproduction, fetal/embryonal development or postnatal development except for common skeletal variations which typically resolve postnatally without intervention. These DART studies provide the first safety data to help inform the use of the vaccine in pregnancy until there are more data in this population. Currently, the Advisory Committee on Immunization Practices has issued recommendation for the use of Pfizer and Moderna for the prevention of COVID-19. Currently, these vaccines have not been tested in pregnant women, thus there are no safety data specific to use in pregnancy. However, the vaccines have shown to be about 95% effective at preventing COVID-19 illness after the second dose.

Small numbers of pregnant people were inadvertently enrolled during vaccine clinical trials of Pfizer/BioNTech (23, including 11 in the vaccine arm) and Moderna (13, including six in the vaccine arm). A miscarriage rate of 8% was reported, with one miscarriage in the Pfizer placebo group and no miscarriages in the vaccine group, along with a rate of 14% with one miscarriage in the Moderna placebo group and 0 in the vaccine group. This provides data, although limited, for no evidence of increased miscarriage risk. The American College of Obstetricians and Gynecologists (ACOG) also recommends that COVID-19 vaccines should not be withheld from pregnant individuals or lactating individuals who meet criteria for vaccination. It is important, although not required, for a conversation to be had between the patient and their clinical team to assist in making decisions regarding the COVID-19 vaccines if possible. Risks and side effects of the vaccine should be explained as part of counselling patients including injection site reactions, fatigue, fever, chills, muscle pain, joint pain and headaches, which are largely a normal part of the body’s reaction to the vaccine caused by the development of antibodies to protect against COVID-19 illness.

There is also currently no evidence that mRNA vaccines affect fertility. According to the guidance issued by the British Fertility Society, there is ‘absolutely no evidence’ that COVID-19 vaccines can affect the fertility of women or men. They also stated that people undergoing in vitro fertilisation, frozen embryo transfer, egg freezing, ovulation induction, intrauterine insemination, donating eggs or sperm could receive the COVID-19 vaccine. However, they recommended separating the date of vaccination from treatment procedure by a few days correctly to attribute symptoms such as fever to vaccine or treatment procedure.

Vertical transmission likelihood

Despite the potential adverse effects to symptomatic women during pregnancy, there is limited evidence of vertical transmission of COVID-19 or of its presence in breastmilk. As of 2 September 2020, 19 neonates were
documented found to be COVID-19-positive based on rtPCR nasopharyngeal swabs. Three of these were febrile, 15 were asymptomatic and one was born at 31 \( \pm 2 \) weeks; he developed disseminated intravascular coagulopathy but was recovering at the time of publication. Thus far, there have been no reported deaths of COVID-19-positive neonates.\(^{25}\)

Angiotensin converting enzyme 2, a target of SARS-CoV-2 cell entry, and the spike glycoprotein of SARS-CoV2 have been found on the syncytiotrophoblast cells of the placental villi that form the interface between mother and fetus in the placenta.\(^{29}\) Therefore, vertical transmission may be possible, unlike with SARS, where no evidence of vertical transmission exists, but it is unclear whether these 19 cases were infected \textit{in utero}, intrapartum or postpartum.\(^{25}\) This study by Pettirrosso et al. also states that the risk of vertical transmission was assessed with rtPCR of nasopharyngeal secretions, placenta, cord blood, amniotic fluid and breast-milk. They found that 19 of 655 nasopharyngeal swabs were COVID-19-positive by rtPCR as discussed and four placenta samples and one cord blood sample were positive, but the neonatal nasopharyngeal swabs were negative. Anti-SARS-CoV-2 IgM and IgG antibodies were elevated in the serum of three neonates, suggesting some hope for antibodies of COVID-19 vaccinated mother’s, passing to the neonate.\(^{25}\) In terms of impacts on the fetus, there is limited data about \textit{in utero} infection, risk of vertical transmission and early positive neonatal testing.

Some studies have shown a linkage of fetal vertical transmission with maternal disease severity, including Penfield et al.\(^{30}\) This study performed rtPCR assays of placental and amniotic membrane samples within 30 minutes of delivery in a series of 11 women who were diagnosed COVID-19-positive during pregnancy and delivered between 1 March 2020 and 20 April 2020. The infants were also tested using rtPCR of nasopharyngeal swabs between day 1 and day 5 of life to assess for COVID-19.\(^{30}\) Three of 11 placental or amniotic membranes swabs of SARS-CoV-2-positive mothers, after caesarean section delivery were positive.\(^{16}\) The three positive placental cases were from mothers in severe stage of the disease, whereas seven of the other eight placentas were negative with mild disease and delivered vaginally. All 11 newborns tested negative for COVID-19 and did not have COVID-19 symptoms such as fever, cough and nasal congestion at the day 1 or day 5 of life. This raises concern that swabs from the placenta and membranes might have been mixed with maternal tissue, amniotic fluid and/or maternal blood.\(^{16}\) Although this was one of the first few studies to demonstrate evidence of SARS-CoV-2 in placental tissue, there was no supported clinical data for vertical transmission.\(^{31}\)

Trostle et al.\(^{32}\) studied 36 pregnant women who had at least one dose of either Pfizer/BioNTech or Moderna since June 2021 and obtained umbilical cord blood at time of delivery. Using the Abbott SARS-CoV-2 assay, 36 neonates (100\%) were positive for antibodies to the spike protein (anti-S IgG) at high titers. All but one of the subjects received both doses of their mRNA vaccines prior to delivery. The neonate born to the woman who received only one dose was still positive for anti-S IgG.\(^{32}\) This study provides support for transplacental antibody transfer following mRNA COVID-19 vaccination during pregnancy with the high levels of anti-S antibodies demonstrated. Given the combination of positive anti-S IgG and negative anti-N IgG (antibodies to the nucleocapsid protein that is only present following natural infection), the neonatal antibodies were secondary to vertical transfer of antibodies from maternal vaccination rather than natural infection.\(^{32}\)

**Unique T-helper 2 bias**

During the first trimester of pregnancy, there is a bias toward T-helper 2 system dominance which protects the fetus by suppressing cell mediated immunity, but leaves the mother vulnerable to viral infections, which are more effectively contained by the Th1 system.\(^{33}\) Data from German and US trials of the Pfizer-Biontech mRNA vaccine (BNT162b2) indicate a broad immune response to the vaccine with induction of neutralising antibody responses as well as helper T-cell type 1 CD4\(^+\) cells and expansion of effector memory CD8\(^+\) T-cells in both men and nonpregnant women participants.\(^{31}\) Currently, there is not enough data to confirm whether pregnant women have the same immunophenotypical response. If so, there are concerns that neonates born to mothers with altered CD4\(^+\) T-cell responses may have long-term sequelae.\(^{31}\) Disruption of the balance of CD4\(^+\) T-cell responses by overstimulation of Th1 immunity may be harmful during pregnancy and is associated with adverse perinatal outcomes; including pre-eclampsia, preterm birth and fetal loss.\(^{31,34}\)

**Impacts on breastfeeding**

In continuation, there are major concerns revolving COVID-19 infection or vaccination and effects on breast milk. Despite ACOG encouragement of the EUA issued by the U.S. Food and Drug Administration, no lactating women were included in the initial trials of vaccine safety and efficacy in the SARS-CoV-19 vaccine trials. Accordingly, few data have been published concerning whether maternal antibodies from the messenger RNA vaccine will be transferred efficiently to neonates through breastmilk. It is essential to address this concern to best advise pregnant individuals, or those considering pregnancy, about prenatal, intranatal or postnatal vaccine recommendation and safe breastfeeding practices. Breast milk contains the nutritional requirements, maternal immunoglobulins, macrophages...
and lymphocytes important for an infant’s development and immune protection.

In the systematic multi-national review of 60 studies, SARS-CoV-2 was not identified in any of the 45 breastmilk samples tested.\(^2^5\) This lack of SARS-CoV-2 detection in breastmilk suggests that the virus may not be excreted via this route, although results of only 45 samples have been reported.\(^2^5\) A study by Wu et al. found a positive viral nucleic acid test in one breast milk sample.\(^3^5\) But when a sample from the infected mother was retested 2 days later, it was found to be negative.\(^3^5\) Similarly, other studies have had little to no success in recovering the virus from previously tested RNA-positive milk samples.\(^3^6\)

A recent systematic review by Centeno-Tablante et al. reported on 77 nursing mothers from 37 studies and concluded that there was no convincing evidence of transmission of SARS-CoV-2 via breastmilk.\(^3^7\) Recently, a group of UMass researchers found that of 15 participants in their study, all of whom had COVID-19 at some point before giving birth, 14 had antibodies in their early breast milk.\(^3^8\) Bilateral colostrum samples were collected from the 15 COVID-19 mothers and exhibited 73% IgA, 73% IgG, and 33% IgM reactivity to the receptor binding domain of the SARS-CoV-2 spike protein. High levels of nine inflammatory markers were also present in the colostrum.\(^3^8\) The presence of these antibodies could indicate a prior infection that elicited a humoral response that cross-reacted with SARS-CoV-2 receptor binding domain. This study provides objective data for the value of initiating breast-feeding despite SARS-CoV-2 infection.\(^3^8\)

One study showed the presence of vaccine-derived IgA antibodies in breastmilk 3–4 weeks post-vaccination with the mRNA COVID-19 vaccines.\(^7\) Golan et al. provided data that mRNA from Pfizer and Moderna vaccines is not detected in human breast milk samples collected 4–48 hours post-vaccine.\(^3^9\) Similarly, Gray et al. recently reported in a prospective cohort study including 131 reproductive age vaccine recipients (84 pregnant, 31 lactating and 16 nonpregnant women) that the COVID-19 mRNA vaccines generated robust humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in nonpregnant women. Vaccine-induced immune responses were statistically significantly greater than the response to natural infection with immune transfer to neonates occurred via placenta and breastmilk.\(^5^0\) A robust induction of IgG, IgA, and IgM after the prime and boost was described. Although the study found that IgA and IgM levels did not increase with the boost, a boost in breastmilk IgG levels, however, was observed after the second dose.

In addition, a longitudinal cohort study of lactating women was conducted by Baird et al. to assess for the transmission of immunity from mothers to neonate through breastmilk.\(^4^1\) The study contained seven participants who were vaccinated with both doses of the Pfizer-BioNTech or Moderna between December 2020 and January 2021. Breast milk samples were collected at pre-vaccination and at 11 additional timepoints, with the last sample at 14 days after the second dose of vaccine. The samples were analysed for SARS-CoV-2-specific immunoglobulins A and G. The results demonstrated the presence of elevated levels of IgA and IgG in breastmilk approximately 7 days after the initial vaccine dose. Comparable to the study conducted by Gray et al., there was an IgG-dominant response. Both studies suggest that vaccination of both pregnant and lactating mothers may prove protective for infants. These studies offer hope that with COVID-19 vaccination and/or breastfeeding post-infection, mothers will be able to pass antibodies on to their fetus and offer protection against this prevalent virus without interrupting breastfeeding.

**Conclusion**

Data collected in the V-safe registry so far include over 50,000 pregnant women with no serious vaccine-related adverse events.\(^7\) The UK has also created a similar registry for its citizens that shows similar results with no safety concerns related to COVID-19 vaccination.\(^7\) Data from Pfizer/BioNTech, Moderna and Janssen vaccines’ animal DART studies have found no safety concerns with no adverse effect on female reproduction, fertility, fetal or embryonal, or postnatal development, miscarriage.\(^7\) It will be essential to continue critically reviewing observational studies, clinical trials and available data for approval of vaccine use in pregnancy.

It is essential that physicians and clinical care teams communicate these findings, explain the risk associated with a COVID-19 infection during pregnancy, and the benefits of vaccination as well as the possible adverse effects. Pfizer-BioNTech recently announced a global phase 2/3 trial in pregnant women which will be the first trials to include expecting mothers in the USA. They aim to enroll around 4000 pregnant women from the USA, Argentina, Brazil, Canada, Chile, Mozambique, South Africa, Spain and the UK. Women over 18 and who are 24–34 weeks into their pregnancy will be eligible.\(^4^2\) The study also plans to follow newborns for 6 months after birth to see whether antibodies from the mother transfer to the infants. Johnson & Johnson subsidiary Janssen is also planning a phase 2 placebo-controlled trial including 824 pregnant females.\(^4^3\) These are exciting endeavours that will hopefully provide further data on safety and efficacy of the vaccine in pregnant populations and effects on their newborns.

Currently, according to data provided by Johns Hopkins, 91 countries have policies that allow for at least some pregnant women to receive COVID vaccines including Greenland, Colombia, Saudi Arabia, Mongolia and Kenya,
whereas 41 countries are recommending against it, including Bolivia, Nicaragua, Algeria, China and Syria. It is imperative that we ensure COVID-19 vaccines will be offered to pregnant individuals in regard to health equity and respecting autonomy. Pregnant patients who decline vaccination should be supported in their decision and, regardless of their decision, the importance of hand washing, physical distancing and wearing masks remains crucial and should be emphasised. We hope that the updated information and evidence-based information collected for this literature review provides the framework to support shared decision-making for pregnant individuals and their healthcare providers.

Disclosures of interests
The authors report no conflicts of interest. This manuscript has not been accepted for publication elsewhere and is not being considered for publication elsewhere. I confirm all authors consent to publication of this work and that all authors have contributed significantly and are in agreement with the content of the manuscript.

Contribution to authorship
All three authors (Joubert, Kekeh and Amin) contributed substantially to conception, acquisition of data, and analysis of data and drafting the article or revising it critically for important intellectual content; have given their final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The magnitude of contributions is reflected in the order authors are listed.

Details of ethics approval
Due to the nature of this literature review ethical approvals were not required.

Funding
No funding was acquired.

Acknowledgements
Not applicable.

Data availability
Data sharing is not applicable to this article as no new data were created or analysed in this study.

Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

References
1. WHO. WHO Coronavirus (COVID-19) Dashboard. Geneva: WHO; 2021.
2. Chaudhary N, Weissman D, Whitehead KA. mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nat Rev Drug Discov 2021. Online ahead of print.
3. Varghese PM, Tsoiaki AG, Yasmim H, Shastri A, Ferluga J, Vatsh M, et al. Host-pathogen interaction in COVID-19: pathogenesis, potential therapeutics and vaccination strategies. Immunobiology 2020;225:152008.
4. Gynecologists TACoOa. American College of Obstetricians and Gynecologists’ Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group: Riley LE, Beigi R, Jameson DJ, Hughes BL, Swamy G, O’Neal Eckert L, et al. Practice advisory: vaccinating pregnant and lactating patients against COVID-19. ACOG Clin 2020.
5. Administration USFD. FDA Approves First COVID-19 Vaccine: Approval Signifies Key Achievement for Public Health. MD, USA: FDA; 2021.
6. Zimmer CCI, Wee S. Coronavirus Vaccine Tracker. NY, USA: The New York Times; 2021.
7. Garg I, Shekhar R, Sheikh AB, Pal S. COVID-19 vaccine in pregnant and lactating women: a review of existing evidence and practice guidelines. Infect Dis Rep 2021;13:685–99.
8. Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586:516–27.
9. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369:77–81.
10. Zhang Y, Zeng G, Pan H, Li C, Kan B, Hu Y, et al. Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine in healthy adults aged 18-59 years: report of the randomized, double-blind, and placebo-controlled phase 2 clinical trial. medRxiv 2020;2020.07.31.20161216.
11. Haj Hussein I, Chams N, Chams S, El Sayegh S, Badran R, Raad M, et al. Vaccines through centuries: major cornerstones of global health. Front Public Health 2015;3:269.
12. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. JAMA 2021;325:1318–20.
13. Farrell R, Michie M, Pope R. Pregnant women in trials of Covid-19: a critical time to consider ethical frameworks of inclusion in clinical trials. Ethics Hum Res 2020;42:17–23.
14. Maykin MM, Heuser C, Feltoych H. Pregnant people deserve the protection offered by SARS-CoV-2 vaccines. Vaccine 2021;39:171–2.
15. Prevention CfDCa. CDC COVID Data Tracker: Unique Populations. Atlanta: Centers for Disease Control and Prevention; 2021.
16. Madjunkov M, Dviri M, Librach C. A comprehensive review of the impact of COVID-19 on human reproductive biology, assisted reproduction care and pregnancy: a Canadian perspective. J Ovarian Res 2020;13:140.
17. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status—United States. Atlanta: Centers for Disease Control and Prevention; 2020.
18. Collin J, Bystroim E, Carnahan A, Ahrine M. Public Health Agency of Sweden’s Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. Acta Obstet Gynecol Scand 2020;99:819–22.
19. Delahoy MJ, Whitaker M, O’Halloran A, Chai SJ, Kirley PD, Alden N, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed. MMWR Morb Mortal Wkly Rep 2020;69:1347–54.
Panagiotakopoulos L, Myers TR, Gee J, Lipkind HS, Kharbanda EO, Ryan DS, et al. SARS-CoV-2 infection among hospitalized pregnant women: reasons for admission and pregnancy characteristics—Eight U.S. Health Care Centers. MMWR Morb Mortal Wkly Rep 2020;69:1355–9.

Zambroano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 Infection by pregnancy status—United States. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.

Narang K, Enninga EAL, Gunaratne MDSK, Ibirogba ER, Trad ATA, Elrefaei A, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. Mayo Clin Proc 2020;95:1750–65.

Verma S, Carter EB, Mysorekar IU. SARS-CoV2 and pregnancy: an invisible enemy? Am J Reprod Immunol 2020;84:e13308.

Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, et al. Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. JAMA Intern Med 2021;181:714–7.

Pettirosso E, Giles M, Cole S, Rees M. COVID-19 and pregnancy: a review of clinical characteristics, obstetric outcomes and vertical transmission. Aust N Z J Obstet Gynaecol 2020;60:640–59.

Moderna. Vaccines and Related Biological Products Advisory Committee Meeting. MD, USA: Moderna; 2020.

Pfizer-BioNTech. Vaccines and Related Biological Products Advisory Committee Meeting. MD, USA: Pfizer-BioNTech; 2020.

ARCS B. BFS & ARCS Covid-19 Vaccines & Fertility. British Fertility Society and Association of Reproductive and Clinical Scientists. UK: British Fertility Society; 2021.

Wiese MD, Berry MJ, Hissaria P, Darby JRT, Morrison JL. COVID-19: can we treat the mother without harming her baby? J Dev Orig Health Dis 2021;9:1–11.

Penfield C, Brubaker S, Limaye M, Lighter J, Ratner A, Thomas K, et al. Detection of SARS-COV-2 in placental and fetal membrane samples. Am J Obstet Gynecol MFM 2020;2:100133.

Klein SL, Creisher PS, Burt I. COVID-19 vaccine testing in pregnant females is necessary. J Clin Invest 2021;131:e147553.

Trostle MEA-RM, Roman AS, Lighter JL. High antibody levels in cord blood from pregnant women vaccinated against COVID-19. AJOG MFM 2021. Online ahead of print.

Dashraath P, Wong JLI, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 2020;222:521–31.

Saito S, Nakashima A, Shima T, Ito M. Review Article: Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol 2010;63:601–10.

Wu Y, Liu C, Dong L, Zhang C, Chen Y, Liu J, et al. Coronavirus disease 2019 among pregnant Chinese women: case series data on the safety of vaginal birth and breastfeeding. BIOG 2020;127:1109–15.

Tryststeen W, Van Cleemput J, Snippenberg WV, Gerlo S, Vandekerckhove L. On the whereabouts of SARS-CoV-2 in the human body: a systematic review. PLoS Pathog 2020;16:e1009037.

Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solon P, Garcia-Casal MN, Rogers L, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Ann N Y Acad Sci 2021;1484:32–54.

Narayanaswamy V, Pentecost B, Alfandari D, Chin E, Minor K, Kastrinakis A, et al. Humoral and cell-mediated response in colostrum after exposure to severe acute respiratory syndrome coronavirus 2. medRxiv 2021:2021.01.03.20248715.

Golan Y, Prahl M, Cassidy A, Lin CY, Ahituv N, Flaherman VJ, et al. COVID-19 mRNA vaccine is not detected in human milk. medRxiv 2021:2021.03.05.21252998.

Gray KJ, Bordt EA, Attey C, Deriso E, Akinwunmi B, Young N, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. AJOG 2021;225:303.E1–17.

Baird JK, Jensen SM, Urba WJ, Fox BA, Baird JR. SARS-CoV-2 Antibodies detected in mother’s milk post-vaccination. J Hum Lact 2021;37:492–8.

Edwards E. Pfizer to Begin Covid Vaccine Clinical Trial in Pregnant Women. New York: NBC News; 2021.

Rubin R. Pregnant people’s paradox—excluded from vaccine trials despite having a higher risk of COVID-19 complications. JAMA 2021;325:1027–8.

Rosen J. Global Policies on COVID-19 Vaccination in Pregnancy Vary Widely by Country According to New Online Tracker. MD, USA: HUB; 2021.