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Safety and Efficacy of Coronavirus Disease 2019 (COVID-19) mRNA Vaccines During Lactation

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Abstract

In this review, we summarize the data on the safety and side effect profile of coronavirus disease 2019 (COVID-19) vaccines during lactation to date, review what is known about mRNA vaccine components in breastmilk, and discuss the efficacy of COVID-19 vaccines in providing immune protection for the breastfeeding infant. The CDC and ACOG recommend lactating individuals receive COVID-19 mRNA vaccines, and stay up to date on booster doses, including the bivalent COVID-19 booster. The lack of serious side effects in mother or infant across numerous large studies and registries of COVID-19 vaccination in pregnancy and lactation is reassuring. While small quantities of mRNA may be transiently detectable in breastmilk after maternal vaccination, there are no data demonstrating that vaccine mRNA can survive the infant GI tract, and no evidence that breastmilk from lactating individuals who have received a COVID-19 mRNA vaccine can cause harm to breastfeeding infants. In contrast, numerous studies demonstrate that breastmilk of vaccinated individuals contains SARS-CoV-2-specific functional antibodies and T-cells, which benefit the breastfeeding infant's developing immune system. Transfer of SARS-CoV-2-specific antibodies from mother to infant is highest when vaccination occurs during pregnancy compared with lactation, as the breastfeeding infant receives both long-lasting antibodies through the placenta and breastmilk antibodies through breastmilk. With clear data demonstrating efficacy and safety, and no data demonstrating harm to mother or infant following COVID-19 vaccine administration during lactation, any recommendations to avoid vaccination while breastfeeding, or withhold breastmilk from the infant for any period of time after vaccination, are not supported by available evidence.

Précis:

Data support the safety and efficacy of coronavirus disease 2019 (COVID-19) mRNA vaccination during lactation; there are no data demonstrating infant harm after ingesting breastmilk after maternal vaccination.

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Introduction

Nearly two years have elapsed since COVID-19 mRNA vaccines initially became available to the public, during which time knowledge about the safety and efficacy of COVID-19 vaccination in pregnancy and lactation has grown substantially. It is well-established that COVID-19 mRNA vaccines are highly immunogenic in pregnant and lactating people,[1-3] and provide excellent protection against severe COVID-19 in these high-risk groups, as they do in the general adult population.[4-6] Receipt of a booster shot generates similar immune responses in pregnant and lactating individuals compared to nonpregnant controls, including against the Omicron variant, and is well-tolerated.[7-9] The Centers for Disease Control and Prevention (CDC) and multiple professional organizations including the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine have consistently recommended vaccination for people who are pregnant or breastfeeding with COVID-19 mRNA vaccines, and have recommended adherence to recommended booster dosing schedules, including with the bivalent COVID-19 vaccine booster.[10-12]

Although COVID-19 vaccination rates in pregnant populations initially lagged that of age-matched groups,[13,14] with critical disparities in vaccine coverage noted in racial and ethnic minority groups,[15] nearly 71% of currently pregnant individuals in the US have completed a primary COVID-19 vaccine series as of November 12, 2022,[16] and many have received booster doses.[17,18] Although serious illness and death from COVID-19 still occurs, with pregnancy being an important risk factor for severe disease,[19] SARS-CoV-2 infection during the Omicron dominant period resulted in less severe disease compared with Delta and pre-Delta epochs in pregnant individuals.[20] This reduced risk of severe-critical disease is attributable not only to differences in strain virulence, but also to higher vaccination rates in pregnant people.

Although the benefits of COVID-19 vaccination during pregnancy are clear, some individuals who are unvaccinated or due for a booster and are hesitant about receiving an mRNA vaccine during pregnancy may consider deferring vaccination to the postpartum period. A pressing question for these individuals has become: what is the optimal time to receive a COVID-19 vaccine that maximizes benefit and minimizes risk to both members of the mother-infant dyad? The recent publication from Hanna et al. in *JAMA Pediatrics*[21] reporting transient detection of small levels of vaccine-derived mRNA in human breastmilk presents an opportunity to review the safety and efficacy of COVID-19 vaccination during lactation. In this review, we aim to: 1) briefly summarize the data on the safety and reactogenicity of COVID-19 vaccines during lactation to date; 2) contextualize the findings of the Hanna et al. study with what is known about mRNA vaccine components in breastmilk; and 3) discuss the efficacy of COVID-19 vaccines in providing immune protection for the breastfeeding infant. Key points are summarized in Box 1.

Safety and side effect profile of maternal COVID-19 mRNA vaccination in lactation

Although pregnant and lactating individuals were excluded from initial COVID-19 vaccine trials,[13,22] at this point in the pandemic, numerous studies including thousands of lactating

individuals receiving mRNA vaccines and their breastfed infants have been reported in the literature; a comprehensive summary of the literature is publicly available on the LactMed database.[23] A search of the NIH/National Library of Medicine's Drugs and Lactation Database (LactMed) conducted in November 2022 revealed no reports in the peer-reviewed literature of serious adverse events in either the breastfeeding recipient of COVID-19 mRNA vaccines, or to the breastfed infant. Side effects are similar in lactating individuals receiving a primary mRNA vaccine series compared with non-lactating individuals, with post-vaccination symptoms more common after the second dose.[1,24-26] Rates of local or systemic post-vaccination symptoms ranged from 56% to 85% among lactating study participants, with pain at the injection site being the most commonly-reported post-vaccine symptom.[24-27] In a large study of over 4400 lactating vaccine recipients, the mRNA-1273 vaccine was consistently more reactogenic than BNT162b2,[24] and in a smaller study of only 86 patients, the Oxford/Astra-Zeneca vaccine (ChAdOx1 nCoV-19) was associated with more post-vaccine symptoms than either of the mRNA vaccines.[28]

No serious adverse events have been reported in breastfeeding infants whose mothers received a COVID-19mRNA vaccine. In an early prospective study of 84 lactating COVID-19 vaccine recipients, 4 subjects reported fever in their breastfeeding infant, although in all cases, fever occurred more than 7 days after maternal vaccination and all infants had symptoms of upper respiratory tract infections, which was thought to be the etiology of the fever.[27] Most subsequent studies reporting outcomes of breastfed infants have been survey-based, which lack a non-vaccinated control group with which to compare and contextualize the responses and are subject to some recall bias. Regardless, these studies report low rates of observed effects in infants, with the most frequent events including changes in sleep or behavior (either increased sleepiness or irritability) and gastrointestinal symptoms, with a range of 1-31% of mothers reporting at least one symptom in these reports.[9,24,25,29,30]

Data are conflicting regarding effect on milk supply after receipt of the COVID-19 mRNA vaccines. A study including over 4400 lactating individuals receiving COVID-19 vaccines, 4% of recipients reported a transient *increase* in milk supply.[24] However, the same study reported a transient *decrease* in milk supply in the days following receipt of a COVID-19 vaccine in 6% of recipients, and other studies have also reported a transient decrease in milk supply in 6-8% of vaccine recipients, with supply returning to normal within 3 days of the vaccine.[24,25,31] Transient changes in milk color have also been reported.[25,31] Available data suggest that lactational concerns may be less frequent following booster doses: in a follow-up survey study of over 10,000 lactating individuals, 96% of individuals reported no lactational concerns after vaccination, with 1.2% reporting any issue with their breastfed infant and 3.5% reporting decreased milk supply.[9] In summary, although transient effects on milk supply and/or infant behavior have been reported following maternal vaccination, the lack of serious side effects in either mother or infant across numerous studies is reassuring.

Human milk extracellular vesicles and vaccine mRNA: detection is not evidence of harm

The COVID-19 mRNA vaccines deliver lipid nanoparticles that encapsulate mRNA encoding the SARS-CoV-2 spike protein to the vaccine recipient's cells. Once taken up by the host cell, the mRNA is released and translated into the SARS-CoV-2 spike protein, which is then processed into peptides that get displayed on the cell surface for immune recognition.[32] Vaccine mRNA has been detected in the plasma of vaccine recipients in low levels in the days following vaccination,[33] so there exists a theoretical possibility that mRNA from the maternal circulation could be excreted intact into breastmilk.

To date, four studies have investigated levels of BNT162b2 or mRNA-1273 mRNA in breastmilk of vaccine recipients.[21,34-36] In a small study of 14 lactating healthcare workers in Singapore receiving the BNT162b2 vaccine, 4 out of 40 breastmilk samples collected within a week of vaccination had detectable levels of vaccine mRNA at low levels (highest concentration of BNT162b2 mRNA was 2 ng/ml, which translates to 0.667% of the original vaccine dose per 100 mL of human milk given to the infant),[35] and a second study of 35 lactating healthcare workers, also in Singapore, receiving a BNT162b2 vaccine detected mRNA (median 70 pg/mL) in 5 of 309 breastmilk samples collected within 1 week of vaccination; all positive samples were collected within 3 days.[36] None of 5 breastfeeding infants recruited had detectable mRNA in their serum. In a small study of 7 individuals who received a COVID-19 mRNA vaccine during lactation in the US, breastmilk was collected 8-48 hours after vaccination, and milk supernatant, fat layer, and cells were tested for vaccine mRNA.[34] Using highly sensitive assays with a lower limit of detection of 0.195 picograms/mL for BNT162b2 and 1.5 picograms/mL for the mRNA-1273 vaccine, none of the 13 samples had detectable vaccine mRNA.

In a recently published study by Hanna et al., breastmilk from 11 lactating vaccine recipients was collected up to 5 days after vaccination and analyzed for the presence of vaccine mRNA in both whole breastmilk and in extracellular vesicles (EVs) isolated from breastmilk supernatant.[21] EVs are particles released from cells that have a phospholipid bilayer and can carry biologically important molecules, including nucleic acids and proteins, in body fluids.[37] The authors report that 5 of 11 samples had detectable vaccine mRNA in breastmilk at levels ranging from 1.3 to 16.8 pg/mL, with mRNA being detectable at timepoints ranging from 1 hour to 45 hours post vaccination. No breastmilk samples had detectable mRNA after 45 hours. Two of 5 positive samples had detectable vaccine mRNA in EVs only.[21] To put these amounts in perspective, even at the highest detected concentration of vaccine mRNA in EVs (16 pg/mL), a 100 mL breastmilk sample would contain at most 0.002% of the amount of mRNA in the mRNA-1273 vaccine.

The study of milk-derived EVs is still relatively nascent. Because human milk EVs have been found to contain various types of RNA,[37,38] it is not surprising that vaccine mRNA would be detected in a greater proportion of breastmilk samples when isolated breastmilk EVs are examined. Evidence is limited, however, as to whether EVs can survive the infant's highly acidic gastric environment or enzymatic digestion of the small intestine. Although a small *in vitro* study suggests such survival is possible, and perhaps key to the potential

biological relevance of breastmilk EVs to the infant,[39] there is no direct *in vivo* evidence that breastmilk EVs can traverse the mucous layer of the intestine and enter the infant blood stream intact.[37] Naked mRNA is highly unstable, subject to rapid degradation by RNases, and poorly taken up by cells in the absence of encapsulation.[40-43] While small quantities of vaccine mRNA in breastmilk may minutely augment the substantial natural EV-RNA cargo, they are unlikely to have biological effects if released. While small quantities of mRNA may be transiently detectable in breastmilk after maternal vaccination, there are no data to suggest harm to the breastfeeding infant.

Benefits of maternal COVID-19 mRNA vaccination to the breastfeeding infant

Pregnant and lactating individuals mount immunologic responses to the COVID-19 mRNA vaccines that are comparable to those of nonpregnant reproductive-aged females.[1,44] Receiving a primary COVID-19 mRNA vaccination series during pregnancy protects the vaccinated mother from serious illness and protects the fetus/neonate by lowering the risk of COVID-19-associated preterm birth.[14,45] Vaccination during pregnancy also provides the infant with protection against COVID-19 hospitalization in the first 6 months of life via transplacental transfer of durable vaccine-derived anti-SARS-CoV-2 IgG, in addition to breastmilk transfer of vaccine-derived IgA, IgM and IgG if the infant is breastfed (Figure 1A).[3,46-48] Receiving a COVID-19 vaccine during pregnancy does not increase the risk of side effects, miscarriage, preterm birth, or fetal growth restriction,[49-51] and may in fact protect against stillbirth.[6] Vaccination during pregnancy has clear benefits for the vaccinated individual and the infant, regardless of breastfeeding status. Despite these benefits, some pregnant individuals remain hesitant about vaccination during pregnancy and choose to pursue vaccination in the postpartum/lactational period, which still is beneficial as it offers protection for the postpartum individual as well as protection for the infant if breastfed. In addition, some individuals who were vaccinated prior to, during, or after pregnancy have become eligible for a booster dose while lactating. To aid with COVID-19 vaccine decision-making in lactating individuals, a conversation of any risks associated with vaccination should be balanced with discussion of the potential benefits breastfeeding provides for SARS-CoV-2-specific and overall newborn immunity.

Human breastmilk plays an important, multifaceted role in providing immune protection to the breastfeeding infant.[52] Although multiple biologically active components of human breastmilk provide non-specific immune defenses, maternal immunoglobulins (Igs) transferred in breastmilk to the lactating infant are key to supporting antigen-specific immunity.[53] Secretory IgA is the most abundant Ig isotype in human breastmilk, although secretory IgM and IgG are also present in breastmilk and play important roles in both immune tolerance and defense against pathogens.[52] By populating and coating the infant's mucosal surfaces, secretory IgA provides barrier immunity by neutralizing pathogens (Figure 1A) [54] and supports the development and maintenance of a healthy gut microbiome through selection of useful commensal bacteria (Figure 1B).[55] Although the roles of breastmilk-derived secretory IgM and IgG are less well understood, IgG has been shown to protect against pathogenic bacteria in the gut as well as respiratory viruses such as

Respiratory Syncytial Virus (RSV),[56,57] particularly in preterm infants who have altered gut permeability.[58]

Multiple studies have demonstrated the presence of SARS-CoV-2 specific IgA and IgG in human breastmilk in the weeks following primary maternal COVID-19 mRNA vaccination during pregnancy and lactation.[59] In one large study of 98 breastfeeding mRNA vaccine recipients, SARS-CoV-2-specific IgA was detected in 89% of samples and IgG in all samples collected 14 days after the second vaccine dose.[60] Studies across multiple cohorts and vaccine platforms consistently demonstrate the presence of SARS-CoV-2 specific IgA and IgG in breastmilk, with breastmilk antibody levels correlating with levels in maternal blood.[59,61,62] The capability of breastmilk from vaccinated, lactating individuals to neutralize the SARS-CoV-2 virus, including variants of concern, has been demonstrated in multiple studies.[62-64] Although SARS-CoV-2-specific IgA and IgG levels decrease over time in breastmilk, levels of both IgA and IgG remain elevated up to 6 months after vaccination.[65,66] In a small study of 10 lactating participants a mRNA booster shot, boosting significantly improves antibody levels and breastmilk neutralizing capability *in vitro*, from 12% to 66% inhibition of the SARS-CoV-2 virus.[67] Although the neutralizing SARS-CoV-2-specific antibodies in breastmilk likely confer some level of protection to the breastfeeding infant, the degree and durability of infant protection that maternal breastmilk antibodies provide is not known. However, these data support the ability of maternal mRNA COVID-19 vaccination to generate significant levels of SARS-CoV-2-specific functional antibodies in breastmilk, which may be boosted by vaccination during lactation.

SARS-CoV-2 specific antibodies detected in the breastmilk of breastfeeding vaccine recipients are transferred to the mucosal surfaces of the breastfeeding infant, and limited evidence suggests they may be capable of transiting beyond the infant's mouth and upper respiratory tract into the lower GI tract. Breastmilk-derived SARS-CoV-2-specific antibodies have been detected in significant amounts in the breastfeeding infants' saliva and stool,[64,65,68] and studies performed *in vitro* support the capability of breastmilk-derived anti-SARS-CoV-2 IgG and secretory IgA to resist degradation in the infant gut.[69,70] Importantly, however, anti-SARS-CoV-2 antibodies have not been detected in the blood of infants whose mothers were vaccinated during lactation only,[29,68] suggesting that maternally-derived antibodies from breastmilk likely do not cross the gut mucosal barrier in detectable quantities. This stands in contrast to antibodies that are transplacentally transferred from mothers vaccinated during pregnancy, which are detectable in the infant's circulation for up to 6 months in the majority of cases.[46] Primary vaccination during pregnancy likely affords more long-lasting infant protection than breastfeeding alone, given that IgG can only be transferred to the newborn circulation via transplacental transfer and not via breastmilk.

Although breastmilk of vaccinated mothers likely confers antibody-mediated neutralization of SARS-CoV-2 that lasts only hours to days after cessation of breastfeeding, there is increasing evidence that breastmilk antibodies play a more complex role in neonatal protection than simple neutralization of pathogens at the mucosal surface. Breastmilk antibodies may serve a more durable immune function in the neonate and infant by helping to establish and maintain the gut microbiome, and training the immune system to "tolerate" antigens at the mucosal surface (Figure 1B).[52] In addition, whether intact immune

cells, which could provide longer-lasting immunity against SARS-CoV-2, can transfer to the breastfed infant is an open question. The presence of SARS-CoV-2-reactive CD4+ T-cells in breastmilk has been demonstrated after maternal vaccination (Figure 1A),[71] with expansion of Spike-specific T-cell receptors in breastmilk observed following a COVID-19 mRNA booster.[72] High levels of mucosal-homing markers in breastmilk T cells suggest that these cells may be derived from a T-cell population residing in the breast tissue itself that are modulated by maternal vaccination.[72] In addition, recent evidence suggests breastmilk-derived maternal cells may be able to traffic across the infant gut mucosa and take up residence in infant tissues.[73] Breastmilk immunity is likely far more complex than simple antibody persistence on infant mucosal surfaces, and the durability of breastmilk-transferred cellular immunity to the infant, as well as breastmilk education of the infant gut microbiome are key areas for future study.[52,74,75] Longitudinal studies of breastfed infants born to vaccinated mothers are needed to better understand the potential short-and long-term protective benefits conferred by breastfeeding.

Future directions and conclusions

A key area for future study is the extent to which enhanced protection of the neonate is afforded by the combination of transplacentally-transferred maternal IgG and breastmilk-acquired IgA, IgM and IgG. As more and more individuals are entering pregnancy vaccinated, it is increasingly important to understand how receipt of a COVID-19 vaccine during lactation complements the transplacental transfer of SARS-CoV-2-specific immunity from prior vaccination. Several studies have demonstrated population of the breastfeeding newborn's gut with protective and functional (e.g. capable of activation of neutrophil phagocytosis) vaccine-induced SARS-CoV-2-specific antibodies,[64,65,68,76] but the extent to which this protection can be augmented by a booster dose during lactation remains unknown. In addition, whether intranasal COVID-19 vaccines, which target induction of mucosal immunity against SARS-CoV-2 and are currently in development,[77] might enhance breastmilk immunity will be important to assess, as some evidence has shown enhanced breastmilk immunity following intranasal influenza vaccination compared with the intramuscular vaccine.[78]

Without any evidence of harm to mother or infant following COVID-19 vaccine administration during lactation, recommendations to avoid vaccination while breastfeeding, or to withhold breastmilk from the infant for any period of time after vaccination, are inappropriate. Although misinformation about the safety of COVID-19 mRNA vaccines in reproduction continues to impact the public's perception of vaccine safety,[79,80] the benefits of COVID-19 vaccination for the mother-infant dyad are clear, whether during pregnancy or lactation, and far outweigh any potential theoretical risks. Pregnant individuals desiring to optimize infant protection against COVID-19 should be encouraged to vaccinate during pregnancy, rather than deferring vaccination until after delivery. As COVID-19 variants become increasingly transmissible over time, pregnant and lactating individuals should be encouraged to stay on schedule with mRNA booster doses, as this remains an important strategy for protecting both members of the breastfeeding pair from COVID-19 disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Key Points

- COVID-19 mRNA vaccination is recommended for lactating individuals (CDC, ACOG).
- Staying up to date on booster doses, including the bivalent COVID-19 booster, is recommended for lactating individuals (CDC, ACOG).
- There is no evidence that breastmilk from lactating individuals who have received a COVID-19 mRNA vaccine can cause harm to breastfeeding infants.
- The breastmilk of vaccinated individuals contains SARS-CoV-2-specific antibodies and T-cells that may benefit the breastfeeding infant's developing immune system.
- How much protection a vaccinated mother's breastmilk affords the breastfeeding infant against COVID-19 and/or severe COVID-19 disease, and how long that protection lasts, is not known.
- Transfer of SARS-CoV-2-specific antibodies from mother to infant is highest when vaccination occurs during pregnancy compared with lactation, as the breastfeeding infant receives both long-lasting antibodies through the placenta and breastmilk antibodies through breastmilk.

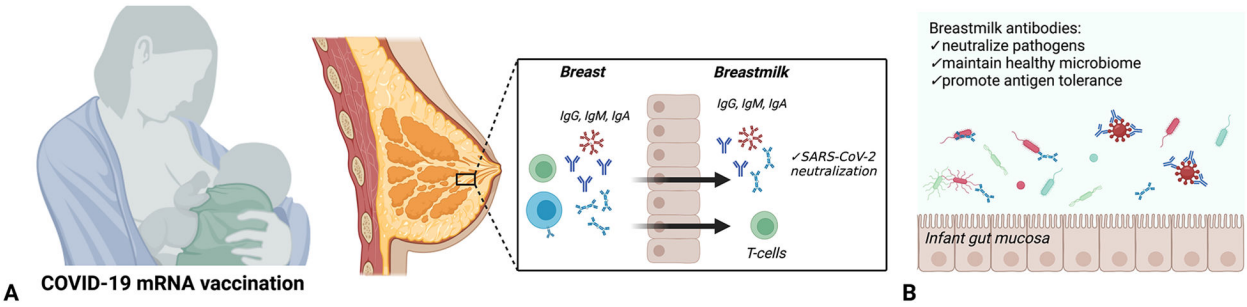

Figure 1:

Coronavirus disease 2019 (COVID-19) vaccine-induced breastmilk antibodies. **A.** Maternal COVID-19 vaccination has been demonstrated to be associated with generation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–specific immune globulin (Ig)G, IgM and IgA, with neutralizing capabilities. In addition, coronavirus disease 2019 (COVID-19) vaccination has been demonstrated to generate SARS-CoV-2–specific T-cells that are detectable in human breastmilk. **B.** Breastmilk antibodies serve diverse functions in the neonatal gut, including neutralizing pathogens, promoting antigen tolerance, and maintaining a healthy gut microbiome through selection of favorable commensal bacteria. Created with BioRender.com.