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COVID-19 Vaccines

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Drug Levels and Effects

Summary of Use during Lactation

Many studies involving hundreds of women and their infants have been reported in the literature. No evidence suggests that receiving a vaccine against SARS-CoV-2 is harmful to either the nursing mother or the breastfed infant. Antibodies and T-cells that neutralize the SARS-CoV-2 virus appear in the milk after maternal vaccination.[1-4] Neutralizing capacity may increase even while antibody levels drop.[5] Nursing mothers experience minimal disruption of breastfeeding after vaccination, which may be related to having systemic symptoms.[6] A few mothers have reported to blue or blue-green discoloration of their milk.[7-11] A small percentage of breastfed infants may experience sleepiness, increased fussiness, fever, rash or self-limiting diarrhea, but no serious adverse effects have been reported. Numerous professional organizations and governmental health authorities recommend that COVID-19 vaccines be offered to those who are breastfeeding because the potential benefits of maternal vaccination during lactation outweigh any theoretical risks.[12-22]

Only a small percentage of milk samples from women who received an mRNA vaccine contain trace amounts of mRNA. mRNA has not been detected in the serum of any breastfed infants.[23-26] mRNA has an estimated serum half-life of 8 to 10 hours and is not detected in milk beyond 48 hours.[23,24,26,27] Moreover, the mRNA in milk is inactive in producing an immune response.[27] The tiny amount of polyethylene glycol-2000 in Pfizer-BioNTech vaccine is not found in breastmilk or absorbed orally, so breastmilk PEG exposure from maternal immunization is not a concern.[28] Neither of the mRNA vaccines available in the US contains a preservative or adjuvant.

Mothers who receive an mRNA vaccine have marked increases in milk antibodies that are similar to or higher than after a COVID-19 infection. Mothers who had a COVID-19 infection during pregnancy and received a vaccine had higher milk antibody levels than those who had either only an infection or two doses of vaccine during pregnancy.[29-31] Pregnancy may increase the anti-spike IgA and IgM antibodies in milk in a second pregnancy after prior vaccination of COVID-19 infection.[32] Milk IgA antibodies develop within 1 to 2 weeks after the first dose, with a loss in activity of 25 to 30% against the Alpha, Beta and Delta variants relative to the original strain. Milk IgG antibody levels are slower to develop after the first dose of an mRNA vaccine in lactating women, but increase after the second dose and persist in milk longer than IgA. In one study, mothers who had lactated for 24 months or longer had more than double the concentration of anti-viral IgG in their milk

than mothers who had breastfed for less than 24 months.[33] Milk antibody levels persist for at least 6 to 8 months after vaccination. There appear to be no major differences in antibody response from the Pfizer-BioNTech and Moderna vaccines, although some studies found a better IgA response to the Moderna vaccine than the Pfizer-BioNTech vaccine.[34-37] Vaccine-induced clones are unique to individuals.[38] Milk antibody response against SARS CoV-2 following the adenovirus vector and inactivated vaccines appear to be considerably weaker than and delayed compared to the mRNA vaccines.[34,37,39-43] One study found the weakest breastmilk antibody response to the CanSino vaccine, compared to the Janssen and Pfizer-BioNTech vaccine.[42]

A booster of the Pfizer-BioNTech or Moderna vaccine markedly increases IgG milk titers, including following an initial vector vaccine, but IgA titers are affected variably.[44-49] A vaccination interval of 3 to 6 weeks appears to generate a better milk antibody response than at 6 to 16 week intervals between vaccinations.[36] Women who had both a SARS-CoV-2 infection and vaccination with an adenovirus vector vaccine (Sputnik V [Gamaleya Institute] or ChAdOx1-S [Astra-Zeneca]) had higher IgA and IgG levels than women who received only a vector vaccine. Women vaccinated with BIBP-CorV (Sinopharm) had similar IgA levels in milk as with the vector vaccine, but lower milk IgG levels.[50]

Some infants have anti-SARS-CoV-2 IgG in their saliva and stool samples after breastfeeding, and although some gastric and intestinal digestion occurs, titers appear sufficient to neutralize SARS-CoV-2.[51,52] Saliva antibodies potentially protect breastfed infants from infection by coating respiratory surfaces. No increase in serum anti-SARS-CoV-2 antibodies are found in infant serum after maternal vaccination unless mothers were vaccinated during pregnancy. The IgG in milk may offer protection to infants against coronaviruses that cause the common cold.[53]

Most lactating persons who received an mRNA vaccine booster reported no adverse effects on lactation or other obstetric concerns.[54] In an on-line survey of persons who received a COVID-19 vaccine (56% Pfizer-BioNTech, 15% AstraZeneca, 9% Moderna), 52 were nursing women with an autoimmune disease. Side effects they experienced were no more frequent than those of healthy control women.[55] A review of adverse reaction reported to the World Health Organization found an increased risk of mastitis in nursing mothers after unspecified (probably various types) COVID-19 vaccines.[56] Some women have reported a small increase in mean menstrual cycle length for cycles in which participants received the first dose (0.5 days) and cycles in which participants received the second dose (0.39 days) of mRNA vaccines compared with pre-vaccination cycles. Cycles in which the single dose of Johnson & Johnson was administered were, on average, 1.26 days longer than pre-vaccination cycles.[57] Another on-line survey of comprising 184 women in Columbia, some reported changes in frequency, regularity duration and volume of menses.[58] Women using a menstrual cycle tracking app reported a less than one day adjusted increase in the length of their first and second vaccine cycles. The change in menstrual cycle length was temporary and there was no change in menses length. The type of vaccine used did not affect the outcome;[59] however, a study using another menstrual tracking app found that the increase in period length occurred only in women vaccinated during their menstrual cycle.[60] Reports submitted to The Netherlands Pharmacovigilance Center found 41.4 reports of menstrual abnormalities per 1000 women who received a COVID-19 vaccine. Amenorrhea or oligomenorrhoea and heavy menstrual bleeding collectively accounted for about half of all abnormalities reported.[61]

Drug Levels

Several vaccines for COVID-19, have been developed. Vaccines available in the US (by Pfizer-BioNTech [Comirnaty] and Moderna [Spikevax]) are messenger RNA (mRNA) vaccines. Another mRNA vaccine is available in Europe (CureVac). Other vaccines (by Janssen-Johnson & Johnson [now off market], Astra-Zeneca, Sputnik-V, and CanSino) are made using human and primate adenovirus vectors. A third type of vaccine available outside of the US is an inactivated whole-virus SARS-CoV-2 vaccine (by Bharat Biotech, Sinopharm and Sinovac). A fourth type, by Novavax contains a synthetic version of the S protein plus an adjuvant and a

synthetic protein subunit vaccine (Abdala) is produced in Cuba. In general, the Pfizer and Moderna vaccines have been studied the most extensively and have the most information on safety in nursing mothers.[62]

mRNA vaccines are genetically engineered messenger RNA strands that encode for a portion of the SARS-CoV-2 S spike or "S" protein and are encapsulated within lipid nanoparticles. These nanoparticles are microscopic spherical-shaped mixtures of specialized fats, cholesterol, and polyethylene glycol that protect and deliver the mRNA strands to the recipient's cells after injection. Once inside the vaccine recipient's cells, mRNA is released, and its genetic code translated into viral S proteins. mRNA does not enter the cell nucleus or alter the cell's DNA. Those proteins are processed into peptides that are displayed on the cell surface, which then stimulates the antiviral immune response.[63] There is no plausible mechanism for intact, complete, functional viral S proteins to be distributed into the milk from the maternal circulation after immunization. Testing of the milk of mothers who received either the Pfizer-BioNTech or Moderna vaccine found little to no mRNA in their milk.

Adenovirus vaccines. These vaccines are made from adenoviruses vectors that have been genetically engineered so they cannot reproduce in the human body. They are also engineered to contain DNA sequences for the S protein. Once inside the vaccine recipient's cells, the DNA is transcribed to mRNA, which is then translated into viral S protein the same as with the mRNA vaccines. The adenovirus vaccines do not require a lipid nanoparticle carrier, and thus contain fewer unique ingredients for the breastfed infant to be potentially exposed to compared to the mRNA vaccines. The Janssen-Johnson & Johnson vaccine contains the solubilizer polysorbate 80, a common food additive, in small amounts that are not expected to be harmful to a breastfed infant.

Whole-virus inactivated vaccines. These vaccines are conventional, killed whole-virus particles prepared in a manner that has been used for decades for various vaccines that are safe for breastfeeding.[64,65] The SARS-CoV-2 virus is grown in a cellular medium and then completely denatured so it is not infectious. When injected, the body creates an immune response against the S protein that is capable of neutralizing the virus if infection occurs.

Maternal Levels. Review articles have compiled data that reported SARS-CoV2-binding antibody levels in milk following a maternal mRNA vaccination against SARS-CoV-2 , mostly with Pfizer-BioNTech and the remainder with Moderna. Studies fairly consistently reported an increase in milk IgA levels within 1 to 2 weeks after the first dose, which remained elevated for several weeks after the second dose. Milk IgG levels usually did not rise appreciably after the first dose, but after the second dose, they increased over baseline and persisted longer in milk than IgA. Milk levels of the antibodies paralleled increases in maternal serum at a lower level. Increases in IgA and IgG in milk were generally greater after the vaccination than after natural infection. IgM levels in milk usually did not increase significantly. It is currently unclear for how long the antibodies persist in milk, but they persist for at least 6 months.[39,53,66-72]

One hundred eighty nursing mothers in the US who received two doses of an mRNA vaccine completed a questionnaire for 7 days after each dose of vaccine. More subjects reported adverse effects after the Moderna vaccine than the Pfizer-BioNTech, especially after the second dose. Milk supply decreased in a small number of women, but it was most prevalent after the second dose of the Moderna vaccine. Between 4% and 8% of mothers noted a change in milk color after a dose of vaccine, usually to a blue-green color.[8]

A prospective cohort study followed 10 lactating healthcare providers who received their first dose of the Pfizer-BioNTech vaccine approximately 5 months postpartum (mean 154 days, range 68–382) and the second dose 21 days later. Maternal serum and milk samples taken 7 and 14 days after the first and second doses found that spike- and RBD-specific IgA and IgG responses in milk closely followed the maternal serum responses, with a peak at 7 days after a dose. IgA was predominant at all time points, but the proportion of IgG increased after the second dose. Neutralization capacity for milk against the spike and RBD proteins was observed in all samples.[1]

In a study of milk antibodies following vaccination with an mRNA vaccine (18 Moderna, 12 Pfizer-BioNTech), IgA antibodies increased after the first injection, but not after the second, whereas IgG increased steadily thought

the 90-day observation time. Microneutralization activity increased throughout time and both IgA and non-IgA (IgG-containing) fractions of human milk exhibited microneutralization activity against SARS-CoV-2 at 90 days post-vaccination.[2]

Mothers who donated to a milk bank in Nevada, USA and who had either a previous positive COVID-19 PCR test (n = 10), a COVID-19 vaccine (12 Moderna, 7 Pfizer-BioNTech) or were unvaccinated with a negative PCR (n = 13) had their milk studied. The milk titers of IgG against the N501Y mutation were higher in the COVID-19 vaccine group than in the no-vaccine group, but comparable with the COVID-19 PCR-positive group. Other antibody titers did not differ between the three groups. The titers of IgA were higher than those of IgM and IgG in all three groups. The titers of IgM and the inhibition by neutralizing antibodies were higher against the E484K mutation than N501Y. Milk neutralizing antibodies did not differ between the three groups, but the neutralizing antibody-binding inhibition of the two mutant receptor-binding proteins to their receptor was higher in the COVID-19 vaccine and PCR groups than in milk from unvaccinated, PCR-negative women.[73]

Twenty-three women who received an mRNA vaccine (2 Moderna, 21 Pfizer-BioNTech) had antibodies and immune cells measured in their breastmilk before receiving a vaccination and after the first and second doses of the vaccine. Both spike-reactive sIgA and spike-reactive T cells were found in the milk after the second dose of vaccine.[3]

A 70-day study of nursing mothers who had either been infected with SARS-CoV-2 (n = 18) or received the Pfizer-BioNTech vaccine (n = 28) found that the average milk IgA levels were similar between the two groups, although the variability in antibody levels was less in those who received the vaccine. Two women who had milk IgA levels before vaccination developed the highest antibody levels in milk.[74]

Twenty-six women who received a Pfizer-BioNTech vaccine and 3 who received a Moderna vaccine were studied. Milk samples were obtained prevaccination and at 1, 3, and 6 months after the first COVID-19 vaccine dose. Twelve of 24 mothers (50%) at 1 month were positive for SARS-CoV-2-specific IgA, 7 of 27 (26%) were positive for IgA at 3 months and 5 of 12 (42%) were positive at 6 months postvaccination. IgG levels were positive for SARS-CoV-2 antibodies at 1 month in 24 of 24 women, 25 of 27 at 3 months and 9 of 12 women at 6 months postvaccination. IgM levels were present in 29% of 24 women at 1 month, 22% of 27 women at 3 months and 8.3% of 12 women at 6 months postvaccination.[68]

Forty-two serum and milk samples were analyzed for the presence of antibodies after receiving two doses of a vaccine against SARS-Co-V-2 (35 Pfizer-BioNTech, 4 Astra-Zeneca, 1 Moderna, and 1 Astra-Zeneca for the first dose and Pfizer-BioNTech for the second dose). Twenty-four milk samples were collected between 20 days and 1 month after the second dose, 10 between 1 and 2 months and 8 between 3 and 4 months after the second dose. Similar to serum, all milk samples had detectable anti-SARS-CoV-2 IgG, and none had detectable IgA.[75] A subset of these women (17 Pfizer-BioNTech, 4 Astra-Zeneca, 1 both) were randomly selected for further study. In these, the level of IgG antibodies in serum was higher than that in breast milk but the complement-system activation potential was retained by milk antibodies, potentially providing additional protection against COVID-19.[76]

Breastmilk samples were obtained from 35 lactating healthcare workers in Singapore who received the Pfizer-BioNTech vaccine, 31 before their first dose and 4 were just before their second dose. All participants completed the 2-dose course within 21 days. Samples were collected on days 1, 3, 7, 14, and 21 after both doses. There were minimal SARS-CoV-2 neutralizing antibodies present in the breastmilk from day 0 to day 3 after the first dose. The neutralizing antibody levels increased markedly at 28 days (day 7 after dose 2). Only samples from 3 mothers did not have detectable neutralizing antibodies at any of the sampling timepoints up to 42 days. Up to day 21 of the first vaccine dose, SARS-CoV-2 spike RBD-specific IgG1 antibody was detected in the breastmilk of 74%, IgA in 100% and IgM in 84% of mothers. After the second vaccine dose, all mothers had detectable

SARS-CoV-2 spike RBD-specific IgG1 and IgA antibody and 89% of mothers had detectable IgM. IgG levels increased markedly 7 days after the second dose and persisted until 21 days after the dose. Five breastmilk samples from 4 mothers had detectable vaccine mRNA, out of 309 samples from 31 mothers tested, with a median concentration of 70 ng/L.[25]

Thirty women who received an mRNA vaccine (20 Pfizer-BioNTech and 10 Moderna). RBD-specific IgA, IgG, and IgM were measured in serial milk samples. Milk samples provided more than 2 weeks after the second dose by 26 of the 30 women were positive for RBD-reactive IgG. Milk samples from only 14 of 30 women were positive for RBD-reactive IgA, and IgM levels were consistently negligible. The levels of Gamma-interferon were higher in milk provided after the first dose and second dose compared with milk provided before receiving the vaccine.[77]

A study of 46 nursing women in Singapore who averaged 13.5 months postpartum and had received the Pfizer-BioNTech vaccine measured the neutralizing IgA antibodies in milk against the original WH-1 strain of SARS-CoV-2 and 4 variants of concern. At 3 to 7 days after the second dose, activity against the Alpha strain was not significantly different from the original WH-1, but activity was reduced by 28 to 33% against the Beta, Gamma and Delta variants. At 4 to 6 weeks after the second dose, activity against all strains was reduced and activity against the Beta, Gamma and Delta variants was reduced by 25 to 30% relative to the original strain.[78]

Twenty-six mother who received an mRNA vaccine against SARS-CoV-2 (Pfizer-BioNTech n = 23, Moderna n = 3) had their milk IgA and IgG levels measured at 30 and 60 days after the second dose. Anti-RBD IgA and IgG antibodies were present in all participants at both time points, although the titers varied considerably among individuals. Fifteen mothers had a higher IgA titer in the first specimen

than the second, two had about the same results in both samples, and nine of them had a higher IgA titer in the second sample. All mothers had anti-RBD IgG in breast milk. All mothers excreted anti-RBD IgG in breast milk. For 14 of the first samples, the measured concentrations were higher than the second sample, in 4 the IgG titers were approximately equal in the first and second samples, and for 8 samples the values were higher in the second specimen.[79]

One hundred twenty-four nursing mothers collected 1650 milk samples over 100 days after their first dose of a COVID-19 vaccine. Mothers who received the Pfizer-BioNTech, Moderna, Janssen and AstraZeneca vaccines were included. Milk was positive for IgA in 96 to 97% of mothers who received an mRNA vaccine (Pfizer-BioNTech and Moderna), but only 39 to 48% of mothers who receive a viral vector vaccine (AstraZeneca and Janssen). Milk was positive for IgG in 96 to all mothers who received an mRNA vaccine at 20 to 30 days after the first dose, but only about 30% of mothers who receive a viral vector vaccine had milk positive for IgG until 90 days after the second dose with the AstraZeneca vaccine. The women who received the Janssen vaccine were not followed beyond about 70 days.[34]

Milk samples (n = 30) were collected daily for one week from 5 mothers who received the Pfizer-BioNTech vaccine. None of the milk samples contained measurable amounts of vaccine mRNA.[80]

Ninety-one women received 2 doses of the Pfizer-BioNTech Covid-19 vaccine during pregnancy at an average of 15.2 weeks prior to delivery. All had their milk analyzed on the third postpartum day and all of them had SARS-CoV-2 RBD spike protein antibodies in breastmilk. The amount of antibody in milk was correlated with maternal serum levels and the trimester of immunization. Antibodies in milk were highest with third trimester vaccination and lowest with first trimester vaccination.[81]

A prospective cohort study of 62 postpartum women who were administered the Pfizer-BioNTech COVID-19 mRNA vaccine during the second or third trimester of pregnancy was performed to measure milk antibody titers. Colostrum had higher levels of IgG, IgA, and IgM than mature milk. The level of IgA in mature milk was

higher when immunization occurred in the second than in the third trimester but, IgG levels in mature milk were higher when immunization was given during the third trimester.[82]

Twenty-three nursing mothers had breastmilk, saliva and serum collected at 30, 60 and 90 days after their first dose of the Pfizer-BioNTech vaccine. The amounts of IgG and IgA in breastmilk were between 10- and 150-fold lower than in serum. IgA was exclusively of the IgA1 isotype, with no production of the mucosal-specific and protease-resistant IgA2.[83]

A 6-month follow-up of nursing mothers who received the Pfizer-BioNTech vaccine found In the 3- and 6-month follow-up, a progressive decrease in milk antibody levels was seen.[84]

Ten women had breastmilk antibody levels measured from the first dose of the Pfizer-BioNTech vaccine to 1, 3, 6, and 9 months after the first dose and 1 month after a third booster dose of the vaccine.

After the primary vaccine series, SARS CoV-2 specific antibodies increased, peaked at 1 month, and then decreased over time. After the booster, human milk SARS CoV-2 specific IgG levels increased from pre-booster levels and were higher than the initial post primary vaccine series peak. SARS-CoV-2 specific IgA levels showed non-significant increases post-booster compared to pre-booster and post-primary vaccine series. IgM levels changed little over the study period.[45]

Women had milk antibody titers after a late third-trimester infection with SARS CoV-2 (n = 28), or two doses of the Pfizer-BioNTech vaccine during pregnancy (n = 11) or lactation (n = 12). Mothers who were vaccinated had higher IgG milk levels than the mothers who had an infection. Mothers infected late in pregnancy had higher SIgA levels in milk than vaccinated mothers.[85]

Thirty-seven women who received either the Pfizer/BioNTech, Moderna, or Johnson & Johnson vaccine were followed for up to 6 months. Milk SARS CoV-2 IgA and IgG levels were higher at 6 months post-vaccination than prevaccination, but both were lower than after 7 to 30 days post-vaccination. Neutralization capacity was higher 6 months after COVID-19 vaccination than pre-vaccination milk. Milk neutralizing capability to SARS-CoV-2 increased over the 6-month time span, even as SARS-CoV-2 specific antibody concentrations decreased.[5]

Serial milk samples were collected by mothers in Hong Kong who either had a SARS-CoV-2 infection (n = 18; 75 samples) or had a vaccination (n = 8; 93 samples) with an unspecified vaccine. Milk IgA antibody levels and neutralizing capacity peaked rapidly after infection or vaccination, with vaccination levels higher. Neutralizing activity was undetectable by about 150 days after the first dose of the vaccine, but a vaccine booster dose restored secretion of neutralizing IgA. Response to the booster varied among vaccinees.[70]

Sixteen women who had a COVID-19 infection and 5 who had received two doses of the Pfizer-BioNTech vaccine during pregnancy had their milk studied. Seven of the previously infected women received a single dose of the Pfizer-BioNTech vaccine postpartum. Mothers who had a COVID-19 infection during pregnancy and received a single dose of the Pfizer-BioNTech vaccine postpartum had higher milk antibody levels than those who had only an infection or two doses of vaccine during pregnancy.[29]

Out of 11 women who were less than 6 months postpartum and received an mRNA vaccine (6 Pfizer-BioNTech, 5 Moderna), mRNA was detected in 7 milk samples from 5 women. The presence of mRNA did not persist beyond 48 hours after the dose.[26]

One hundred-ten breastfeeding mothers who were vaccinated with either two doses of the Pfizer-BioNTech (n = 70) or Moderna (n = 20) vaccine or one dose of the Astra-Zeneca vaccine (n = 20) provide milk samples at 30 days and 6 months after their last dose. Only 62 mothers were still nursing at 6 months postpartum. Anti-SARS-CoV-2 IgA and IgG antibodies were detected in breastmilk 6 months after receiving the second dose, although their concentrations were lower than concentrations at 30 days after vaccination.[71]

A study of nursing mothers who received three doses of an mRNA vaccine while breastfeeding found that milk anti-spike IgG levels increased and were higher than their levels following the second dose. Milk anti-spike IgA levels also trended higher after receipt of the 3rd dose but was not statistically significantly increased over pre-boost levels and their levels were similar to the post-second dose timepoint.[86]

Twenty women who had received two doses of an mRNA vaccine (17 Pfizer-BioNTech, 3 Moderna) against SARS-CoV-2 had milk samples collected before and about 1 week after the third vaccine dose. Breastmilk cells were collected. Breastmilk contained higher frequencies of T effector and central memory populations that expressed mucosal-homing markers than maternal blood. T cell receptor sequence overlap was limited between blood and breastmilk. Overabundant breastmilk clones were observed in all individuals, including to SARS-CoV-2 spike. SARS-CoV-2 spike-specific T cell receptors were more frequent in breastmilk compared to blood and expanded in breastmilk following a third mRNA vaccine dose.[4]

Twenty-six lactating women received a booster dose of an mRNA vaccine (all but one Pfizer-BioNTech). Thirteen had received an mRNA-based vaccine, namely BNT162b2 (n = 4) or mRNA-1273 (n = 9) initially and the other 13 participants previously completed a vaccination regimen with a vector-based vaccine,(8 AstraZeneca, 5 Janssen). Homologous and heterologous booster vaccination induced a similar change in IgA and IgG antibodies in human milk during the follow-up period. Participants who received homologous booster vaccination had overall higher levels of SARS-CoV-2-specific IgA and IgG in their human milk than those who received heterologous booster vaccination, due to overall higher pre-booster levels.[47]

Sixty-one volunteers (45 SARS-CoV-2 naive, 16 SARS-CoV-2 recovered) received two doses of the Pfizer-BioNTech vaccine 3 weeks apart. Four women were breastfeeding and provided milk and blood samples. Anti-RBD IgG antibodies were detected in the milk of the breastfeeding women in a pattern similar to their serum levels.[87]

Women who received a primary COVID-19 vaccine during pregnancy (n = 24) or lactation (n = 21) and received a booster vaccine had milk samples taken to measure SARS-CoV-2 anti-nucleoprotein (NP) and anti-receptor binding domain (RBD) IgG and IgA in their milk. The mothers almost exclusively received mRNA vaccines for both their primary and booster doses. Anti-RBD IgG and IgA in milk remained increased through 120 to 170 days after the booster vaccine and did not differ by maternal NP status.[48]

Sixty-three lactating mothers received a Covid-19 mRNA vaccine (57% Moderna and 43% Pfizer-BioNTech). Vaccination led to breast milk secretory IgA (sIgA) and IgG antibodies with consistent viral neutralizing activity. Milk sIgA titers increased further after second vaccination. Twenty-two received a third booster dose and sIgA titers were increased in all who received it and were detectable even 6 months after the third vaccine dose, including women with extended breastfeeding beyond 12 months. Milk IgG antibody titers were higher and more sustained than sIgA. Antibody titers were not associated with individual dyad characteristics or vaccine manufacturer.[88]

Forty-nine lactating mothers in Hong Kong provided milk samples one week after their first and second doses and 1 month after their second dose of the Pfizer-BioNTech vaccine. Peak milk antibody levels occurred 1 week after the second dose. The composition of the human breast milk microbiota changed dynamically throughout the vaccination regimen, but the abundances of beneficial microbes such as *Bifidobacterium* species did not significantly change after vaccination.[89]

A single-center prospective cohort followed 11 nursing mothers who received a primary series of mRNA SARS-Co-V2 vaccine. IgG and IgA titers increased in breastmilk following each dose, peaking 1 to 4 weeks after series completion. But it did not induce neutralizing antibodies against Omicron BA.4/5. Titers remained elevated for 7 to 9 months, except for in breast milk IgA which returned to baseline within 1 month.[90]

Cuban women vaccinated with 3 doses of a synthetic protein subunit vaccine (Abdala) during pregnancy had milk antibody titers measured. Fifty milk samples were collected 5 weeks after the third dose of the vaccine and 53 were obtained 9 weeks from the 103 women. Antibody levels were compared to those in the milk of 52 nonvaccinated women at least 40 days after the positive RT-PCR- test in women who had contracted COVID-19. High levels of anti-RBD IgA antibodies were detected in breastmilk samples 9 weeks after vaccination and anti-RBD IgG antibodies rose from the fifth to the ninth week. In the post-COVID-19 mothers, the IgG-type response was higher than in both post-vaccination periods. Neutralizing antibody titers were similar in breastmilk from vaccinated and COVID-19 recovered women.[91] An extension of this study found that in these same women, their breastmilk antibodies neutralized OmicronBA.5 RBD, although not to as great an extent as the original Wuhan strain.[92]

A study in Thailand compared antibody responses between women who had previously had a COVID-19 infection, a COVID-19 infection plus vaccination or only vaccinated. Vaccinated patients had received a variety of vaccine types. sIgA, sIgG and neutralizing antibodies in milk persisted in for 6 months, no differences in sIgA, sIgG, and neutralizing antibodies observed between lactating mothers receiving two, three, or more than three doses, although mothers who had the infection and vaccine(s) had higher in vitro sIGa and neutralizing antibody titers at 3 months than those who had vaccination alone.[72]

Infant Levels. Sixty-one women vaccinated postpartum with the Pfizer-BioNTech vaccine. SARS-CoV-2 IgG was detected in the oral mucosa of 3 of 5 breastfed infants. None of 21 infants who had serum samples taken had anti-SARS-CoV-2 IgG detected.[93]

A study reported 8 breastfed infants of mothers who received an mRNA vaccine against SARS-CoV-2 at ages between 68 days and 1 year of age. No anti-SARS-CoV-2 IgG, IgM or anti-RBD IgA antibodies were detected in the serum of any of the infants 4 to 10 weeks after the second maternal vaccination.[28]

A study of 31 mother-baby pairs examined the levels of SARS-CoV-2-specific IgA in the blood, and noses of infants whose mothers had received a COVID-19 vaccination either antepartum (Pfizer n = 9, Moderna n = 9) or postpartum (Pfizer n = 6, Moderna n = 7). All infants had detectable total (non-antigen specific) IgA and IgG in the nasal samples, and no significant differences in total IgG, IgA, or IgA/IgG ratio were noted between the two groups, though total IgA was higher than total IgG in both groups. Anti-spike IgG was more frequently detected from the nares of breast milk fed infants in the antepartum group than postpartum group (89% vs. 0%). In the antepartum group, 33% of infants had high anti-spike IgA titers in the nares, whereas none of the infants in the postpartum group had detectable anti-spike IgA in the nares.[94]

Five infants of nursing mothers who received the Pfizer-BioNTech vaccine had a single serum sample collected at a median of 48 days (IQR 44-57) after the second maternal vaccine dose. The age of these infants at the point of maternal vaccination ranged from 3 to 20 months. Of the 5 infants, one was from a mother with detectable vaccine mRNA in both breastmilk and serum and another three were from mothers with vaccine mRNA in the serum. None of the infants had detectable neutralizing antibodies or vaccine mRNA in their serum.[25]

Breastfed infants of 30 women who received an mRNA vaccine (20 Pfizer-BioNTech and 10 Moderna) had stool samples collected 21 days after the second maternal dose. Anti-RBD IgG and anti-RBD IgA were detected in 33% and 30% of infant stool samples, respectively.[77]

Thirteen breastfed infants of Covid-19 naïve mothers who received the Pfizer-BioNTech vaccine had blood samples obtained at 8 weeks after the first maternal dose of the vaccine. Anti-S SARS CoV-2 IgM and IgA antibodies were detected in only 1 of the 13 infantile serum samples. None contained anti-S SARS CoV-2 IgG above the cut-off specified by the manufacturer.[95]

Twenty-three breastfed infants had feces and pharyngeal swabs collected at 30, 60 and 90 days after their mother's first dose of the Pfizer-BioNTech vaccine. Only traces of antibodies were retrieved from the feces of breastfed infants, and no IgG nor IgA were retrieved from infants' buccal swabs.[83]

A study of 13 mother-infant pairs found that 6 to 12 months after two doses of the Pfizer-BioNTech vaccine postpartum, SARS-CoV-2 S IgG antibodies in serum was positive in only two of the infants.[96]

Twenty-five breastfed infants whose mothers received either the Pfizer/BioNTech, Moderna, or Johnson & Johnson vaccine were followed up to 6 months. The infants' stool levels of SARS-CoV-2 IgA and IgG were higher than pre-COVID negative controls.[5]

Eleven infants of mothers who had received two doses of an mRNA vaccine had saliva samples taken between 0 and 3 hours after nursing. Anti-spike IgA levels were higher in infant saliva over time after feeding compared to IgG antibodies, with 6/11 (55%) infants having detectable antibodies immediately after breastfeeding and 3/11 (27%) infants remaining positive at all time points until the next feeding. IgG antibodies were less abundant in the infant's saliva after feeding.[86]

Infants of women who received a primary COVID-19 vaccine during pregnancy (n = 24) or lactation (n = 21) and received a booster vaccine had blood samples taken to measure SARS-CoV-2 anti-receptor binding domain IgG and IgA in their blood. The mothers almost exclusively received mRNA vaccines for both their primary and booster doses. Anti-RBD IgG and IgA did not increase in infant blood after maternal booster.[48]

Sixty-three nursing mothers received a COVID-19 mRNA vaccine (57% Moderna and 43% Pfizer-BioNTech). Fifty-two of their infants had serum collected for SARS-CoV-2 antibodies. The antibodies were detected only if their mothers had a COVID-19 infection or vaccination during pregnancy.[88]

Effects in Breastfed Infants

In a cohort study of 180 women who received an mRNA vaccination (71% Pfizer, 29% Moderna) against SARS-CoV-2, some mothers reported side effects in their infants following vaccination. The most common events following the second dose were irritability (10.3% and 10.4% for Pfizer and Moderna, respectively), poor sleep (7.8% and 8.3% for Pfizer and Moderna, respectively), and significantly more drowsiness in children whose mothers received Moderna than Pfizer (6.4% and 0%, respectively).[8] It is not known if these side effects were caused by the vaccine.

Twenty nursing mothers received 2 doses of an inactivated virus vaccine (CoronaVac, Sinovac). None of their breastfed infants had any adverse effects reported.[97]

An on-line survey of 4455 nursing mothers who received either the Pfizer-BioNTech or Moderna vaccine found that 7.1% of mothers reported an adverse effect in their breastfed infant. The most frequent symptoms were increased sleepiness and increased fussiness, both at about 3% of infants, with the frequency greater after the second dose. Less frequently reported side effects included fever, rash, diarrhea, vomiting, changes in feeding frequency, and other miscellaneous symptoms. All were numerically, but not statistically more frequent after the second dose.[7]

A study found that among the breastfed infants of 50 women who receive an mRNA vaccine against COVID-19 during pregnancy or lactation, none had any serious adverse effects. A few reports of minor sleep changes and gastrointestinal symptoms were reported after the first dose of vaccine, but 88% of women reported no infant side effects. None of the infants had any reported symptoms after the second dose.[28]

A prospective study was performed in 88 lactating healthcare workers in Singapore given the Pfizer-BioNTech vaccine for COVID-19. No adverse events (fever, rash, cough, behavioral change, vomiting, or diarrhea) were reported by mothers among infants who were breastfed after maternal vaccination.[9]

Ninety-four mothers who received either the Pfizer-BioNTech or Moderna vaccine completed a questionnaire daily for 14 days after the second dose of the vaccine. Thirty-one percent of mothers observed some event in their breastfed children. Most frequently the children were irritable. During the 14 days of follow-up, 36% of the children were diagnosed with respiratory infection, which could have explained their effects. No infants developed serious adverse events nor were they diagnosed with COVID-19 within the study period.[98]

A 16-month-old breastfed infant developed a fever and a rash on her face and extremities 2 days after vaccination of her mother with the first dose of the Astra-Zeneca vaccine. The rashes disappeared by day 7 after the injection. After the second dose of the Astra-Zeneca vaccine, the infant had a brief fever 2 days after her mother's dose, but no rash . The authors considered the rash to be possibly related to the vaccine, but not conclusively.[99]

In a follow-up of 10,278 lactating individuals who received a booster dose of either the Pfizer-BioNTech or Moderna vaccine, 121 (1.2%) reported any issues with their breastmilk-fed infant after vaccination.[54]

An on-line survey of mothers in Mexico who received a COVID-19 vaccine (Pfizer–BioNTech, AstraZeneca, CanSinoBIO, Sinovac, Sputnik V, Janssen, or Moderna) found that more symptoms were reported in infants aged 4.1 to 6 months and in those who received the Sinovac vaccine. The most commonly reported side effects in breastfed infants were irritability (2.3%), fever and diarrhea (2.5% each).[100]

None of 26 breastfed infants were reported to have had any side effects after their mothers' third dose of an mRNA vaccine.[86]

A multicenter survey of 750 breastfeeding women in Bangladesh who received two doses of a COVID-10 vaccine (Pfizer-BioNTech, Moderna, Sinovac, Oxford-AstraZeneca, Johnson and Johnson, or Covaxin) found that only 8 women reported that their infant had symptoms such as fever or runny nose after the mothers received the vaccine. No women reported cough, sore throat, rash, vomiting or diarrhea in their infants.[101]

Effects on Lactation and Breastmilk

In a cohort study of 180 women who received an mRNA vaccination (71% Pfizer, 29% Moderna) against SARS-CoV-2, some women reported a temporary reduction in milk supply. The percentages of women who reported a decrease in milk supply after the Pfizer vaccine was 7.3% and 8% after the first and second doses, respectively. The percentages of women who reported a decrease in milk supply after the Moderna vaccine was 8% and 23.4% after the first and second doses, respectively. The difference between the two vaccines was statistically significant after the second dose. In all cases, the milk supply returned to normal within 3 days. A few women reported an increase in milk supply after each dose. Five women reported a change in milk color to blue-green after a dose of vaccine.[8]

In an on-line survey of 4455 nursing mothers who received either the Pfizer-BioNTech or Moderna vaccine, 3.9% reported an increase in milk production and 6% reported a decrease in milk production. The remainder of mothers reported no change in milk production.[7]

A prospective study was performed in 88 lactating healthcare workers in Singapore given the Pfizer-BioNTech vaccine for COVID-19. No participant reported a change in milk supply. One reported a transient bluish-green tinge to her milk color after her first vaccine dose but not after her second dose.[9]

A teratology information service in the Netherlands received reports of 194 women who experienced a decrease in milk supply after receiving the COVID-19 vaccine (89% Pfizer-BioNTech). The median time to the decrease was one day and the median duration was 4 days. Ten percent of women reported complete cessation of breastfeeding. These mothers had infant who were a median of 5.25 weeks old compared with 8 weeks for the entire cohort.[69]

A survey of 1784 lactating women in Singapore who received either the Pfizer-BioNTech (79% of respondents), Moderna, Sinovac or Astra-Zeneca vaccine found that 5.6 to 14.4% of women reported either an increase or decrease in milk supply. Those who received non-mRNA vaccines were less likely to report any change in milk supply or soreness in the breasts compared to those who received mRNA vaccines. Exclusively breastfeeding women were more likely to report breast engorgement and changes in breast milk supply. Symptoms lasted a median of 3 days. Overall, 2.3% and 2.4% of women reported a change in milk color following one or two doses, respectively.[102]

A prospective study was performed with 382 breastfeeding physicians in Italy who received the Pfizer-BioNTech Covid-19 vaccine. Among infants of breastfeeding mothers, 6 experienced fever, 5 rash and 4 moderate and self-limiting diarrhea.[103]

In a follow-up of 10,279 lactating individuals who received a booster dose of either the Pfizer-BioNTech or Moderna vaccine, 83 (0.8%) reported an increase in milk supply, and 355 (3.5%) reported a decrease in milk supply.[54]

Twenty-six women who had 2 doses of a COVID-19 vaccine (23 Pfizer-BioNTech and 3 Moderna) provided milk samples at 30 and 60 days after their second dose. Ten cytokines were measured in milk and compared to the milk of control mothers and women who had contracted mild COVID-19. The cytokines were TNF-alpha, IFN-beta, IL-1beta, IL-2, IL-5, IL-6, IL-10, IFN-gamma, GM-CSF, and IP-10. There were no differences in the concentrations of any of the cytokines in any of the groups at any time.[104]

An analysis of 6,474 reports in the World Health Organization's VigiBase associated with COVID-19 vaccine during lactation was performed. Reactions coded as "functional lactation disorders" showed a significant disproportionate reporting for COVID-19 vaccines during lactation. Further analysis indicated that this was associated with a 2.76 fold risk of mastitis.[56]

A multicenter survey of 750 breastfeeding women in Bangladesh who received two doses of a COVID-10 vaccine (Pfizer-BioNTech, Moderna, Sinovac, Oxford-AstraZeneca, Johnson and Johnson, or Covaxin) was performed. One woman reported a reduction in milk supply, two reported breast engorgement and one reported breast soreness following vaccination. None reported a change in milk color. [101]

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Substance Identification

Substance Name

COVID-19 Vaccines

Drug Class

Breast Feeding

Lactation

Milk, Human

Vaccines