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COVID-19 Drugs and Breastfeeding Update

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Many products are being investigated for prevention and treatment of COVID-19, and a few have been formally approved. This column updates a 2020 column[1] on this topic and reviews the use in breastfeeding of the most prominent therapies used against the SARS-CoV-2 virus. Additional breastfeeding references on specific drugs can be found in the corresponding LactMed records.

Vaccines

Vaccines against SARS-CoV-2 are the most effective preventative agents for COVID-19. Dozens of studies involving hundreds of women and their infants have been published. Evidence strongly indicates that SARS-CoV-2 vaccines are not harmful to either the nursing mother or the breastfed infant. 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.

Several vaccines for COVID-19 have been developed. Vaccines available in the United States (by Pfizer-BioNTech and Moderna) are messenger RNA (mRNA) vaccines; another mRNA vaccine is available in Europe. Other vaccines (by Janssen-Johnson & Johnson, Astra-Zeneca, and others outside the United States) are made using human and primate adenovirus vectors. A third type of vaccine available outside of the United States is an inactivated whole-virus SARS-CoV-2 vaccine (by Bharat Biotech, Sinopharm, and Sinovac).

Only a small percentage of milk samples from women who received an mRNA vaccine contained trace amounts of mRNA from the vaccine, and mRNA has not been detected in breastfed infants among a few infants tested. mRNA from the vaccine has an estimated serum half-life of 8–10 hours. The tiny amount of polyethylene glycol (PEG)-2000 in the Pfizer-BioNTech vaccine is not found in breast milk or absorbed orally, so breast milk PEG exposure from maternal immunization is not a concern. Neither of the mRNA vaccines available in the United States contains a preservative or adjuvant.

Mothers who receive an mRNA vaccine have marked increases in milk T cells and immunoglobulin (Ig) that are similar to or higher than after a COVID-19 infection. Milk IgA antibodies develop within 1–2 weeks after the first dose, with a loss in activity of 25–30% 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, 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 antiviral IgG in their milk than mothers who had breastfed for less than 24 months.

There appear to be no major differences in antibody response from the two mRNA vaccines available in the United States. Milk antibody response against SARS CoV-2 following the adenovirus vector and inactivated vaccines appears to be considerably weaker than with the mRNA vaccines.

Some infants have anti-SARS-CoV-2 IgG in their saliva and stool samples after breastfeeding. Salivary antibodies potentially protect breastfed infants from infection by coating respiratory surfaces. No increase in anti-SARS-CoV-2 antibodies are found in infant serum after maternal vaccination unless mothers were vaccinated during pregnancy. Nursing mothers usually experience minimal disruption of breastfeeding after vaccination although a few reported transient blue or blue-green discoloration of their milk.

Remdesivir

Remdesivir is fully approved by the U.S. Food and Drug Administration (FDA). It inhibits viral RNA replication by blocking RNA-dependent RNA polymerase. It is moderately effective in reducing symptoms and hastening recovery in hospitalized patients with severe infections. The drug is given intravenously for 5 days, primarily for patients hospitalized with severe COVID-19; the duration may be extended up to 10 days in those who have not improved after 5 days of treatment. Remdesivir is given by intravenous (IV) infusion because it is poorly absorbed orally, so infants are not likely to absorb clinically important amounts of the drug from milk, although oral bioavailability of the drug's active metabolite is not known.

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A few newborn infants have received IV remdesivir therapy for Ebola with no serious adverse drug reactions. The drug is not contraindicated in nursing mothers, but until more data are available, remdesivir should be used with careful infant monitoring during breastfeeding. The most common adverse effects reported in drug recipients include elevated aminotransferase and bilirubin levels and other liver enzyme elevations, diarrhea, rash, renal impairment, and hypotension. Infusion-related and anaphylactoid reactions have been reported in drug recipients, but these are unlikely to occur in breastfed infants who would receive the drug orally.

Oral Antivirals

Two oral antivirals have received emergency use authorization (EUA) for prehospitalization use against the SARS-CoV-2 virus in the United States. Neither has been studied in nursing mothers, but EUA information differentiates them somewhat from each other.

Molnupiravir has authorization for patients over 18 years with positive results of direct SARS-CoV-2 viral testing and those who are at high risk for progression to severe COVID-19 when alternative COVID-19 treatment options cannot be used. It is only modestly effective in preventing serious disease and hospitalization. Based on animal studies that found fetal harm, use in pregnant women is discouraged. Although not contraindicated, breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir, perhaps because of the animal pregnancy data.

Nirmatrelvir is a nucleoside analog that is more effective against COVID-19 than molnupiravir. It is taken together with ritonavir, which is used to enhance nirmatrelvir's bioavailability. The combination has EUA for those aged 12 and older with mild-to-moderate COVID-19 with positive results of direct viral testing and who are at high risk for progression to severe COVID-19.

The EUA for nirmatrelvir recommends weighing the benefits and risks of breastfeeding with the drug, which is a weaker warning than with molnupiravir, and it appears to be based on a lack of safety data rather than any adverse reaction concern. Ritonavir has been studied in breastfeeding mothers being treated for HIV infection. It is excreted into milk in low concentrations, and low levels can be found in the blood of some breastfed infants. No adverse reactions in breastfed infants have been reported with ritonavir. Because of the poor oral bioavailability of nirmatrelvir and small amounts of ritonavir in milk, this combination is unlikely to adversely affect the nursing infant.

Favipiravir

Favipiravir is a viral RNA polymerase inhibitor approved for influenza overseas that is being tested for use against COVID-19. It is not approved by the FDA nor does it have EUA in the United States. In clinical trials, favipiravir has been well tolerated, but has caused liver enzyme abnormalities, gastrointestinal symptoms, and serum uric acid elevations. One unique feature of favipiravir is that it is contraindicated for use in pregnant women because of animal teratology studies. Men taking the drug are recommended to avoid intercourse with pregnant women during treatment and for at least 7 days after the last dose.

One nursing mother who had COVID-19 was prescribed favipiravir 1,600 mg twice on the first day, then 600 mg twice daily for 4 days. She breastfed her 15-month-old COVID-19-negative infant just before each dose of the drug. She pumped and discarded her milk between doses. No symptoms were observed in the baby during maternal drug use, and no abnormalities were detected in the baby's hematological and biochemistry tests. The infant who was partially breastfed was followed for 6 months and did not develop any symptoms.[3]

Antibody Therapy

Several forms of antibody therapy have received EUA by the FDA since the start of the pandemic, but some of them have had their EUA rescinded because they were not effective against newer variants, such as Omicron.

The distribution of the ''antibody cocktail'' of bamlanivimab and etesevimab was stopped in June of 2021, and distribution of a similar combination of casirivimab and imdevimab was stopped in January of 2022, both because of a lack of efficacy against newer viral strains. Currently, two single-antibody products with EUA have activity against the Omicron variant: bebtelovimab and sotrovimab.

Monoclonal antibodies have very low levels in breast milk because of their high molecular weight, and they are poorly bioavailable in breastfed infants because they are partially destroyed in the infant's gastrointestinal tract, at least after the first few days postpartum.[2] Concerns with monoclonal antibodies against SARS-CoV-2 during breastfeeding with these drugs are minimal, and the antibodies might even be beneficial for the breastfed infant if they do enter the milk.

Convalescent plasma is a polyclonal antibody mixture obtained from the blood of persons who have recovered from COVID-19. Similar to monoclonal antibodies, this product is unlikely to harm breastfed infants.

Tocilizumab is an anti-inflammatory monoclonal antibody that is used in patients hospitalized with severe COVID-19 disease. Only small amounts of tocilizumab were detected in breast milk after IV doses in several mothers being treated for rheumatoid arthritis and related conditions. A few mothers have breastfed their infants with undetectable infant serum levels and no reported adverse effects.

Corticosteroids

Moderately high-dose corticosteroids, primarily dexamethasone and methylprednisolone, have been used to treat hospitalized patients with COVID-19. Although these patients are unlikely to be breastfeeding their infants, harm to the infants from corticosteroids in milk is not a concern. Amounts of methylprednisolone in breast milk are very low, and no adverse reactions in breastfed infants have been reported, even with IV doses as high as 1 g. No data are available on dexamethasone in breast milk. Some studies have found a decreased milk supply in mothers treated with high-dose corticosteroids.

Unauthorized Drugs

Ivermectin inhibits SARS-CoV-2 in vitro, possibly by inhibiting nuclear transport activity. Although some initial meta-analyses of moderate-quality published data indicate that ivermectin might result in reductions in COVID-19

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deaths and using ivermectin early in the disease may reduce progression to severe disease, the FDA considers that currently available data do not show ivermectin to be effective against COVID-19.[4–6] Furthermore, there are reports of overdoses of ivermectin in people taking veterinary and topical formulations of ivermectin to treat or prevent COVID-19. Symptoms included hypotension and neurologic effects such as decreased consciousness, confusion, hallucinations, seizures, coma, and death.

Data from four nursing mothers indicate that ivermectin is poorly excreted into breast milk after a single oral dose. Amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants, but no data are available on the repeated doses used to treat COVID-19.

The antimalarials chloroquine and hydroxychloroquine were prominent in the news earlier in the pandemic, but these drugs have not performed well against COVID-19 in controlled clinical trials. The FDA issued a Drug Safety Communication warning against use of chloroquine outside of a clinical trial because of the risk of serious cardiac arrhythmias, including QT prolongation and it is not recommended for treatment of outpatients. Very small amounts of chloroquine and hydroxychloroquine are excreted into breast milk; however, hydroxychloroquine data in breastfeeding are more robust. In infants up to at least 1 year of age, careful follow-up found no adverse effects on growth, vision, or hearing.

Azithromycin has been used alone and with hydroxychloroquine for COVID-19. Meta-analyses found that azithromycin is ineffective alone and actually increases mortality when used with hydroxychloroquine in hospitalized patients.[7] Although it should not be used to treat COVID-19, only low levels of azithromycin appear in breast milk and it is used in infants in higher doses than appear in milk. Monitor infants for possible effects on the gastrointestinal flora, such as vomiting, diarrhea, and candidiasis (i.e., thrush, diaper rash). Unconfirmed epidemiologic evidence indicates that the risk of infantile hypertrophic pyloric stenosis might be increased by maternal use of macrolide antibiotics, but this relationship is questionable.

Summary

Several proven modalities are available for COVID-19 prevention and treatment. For prevention, vaccines are particularly effective and safe to use in nursing mothers. For treatment, monoclonal antibodies are safe, and remdesivir, nirmatrelvir, and corticosteroids appear to pose low risk to the breastfed infant.

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