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ORIGINAL ARTICLE

## Breastfeeding and Treatment for Coronavirus infection 2019 (Covid-19)

### *Aleitamento materno e terapêutica para a doença coronavírus 2019 (COVID-19)*

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Breast Feeding,  
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#### Abstract

In the recent COVID-19 pandemic, it was recommended to continue breastfeeding by women with suspected or confirmed diagnosis of infection. In this case, biosafety care must be adopted to prevent the transmission of the disease to the newborn. Review of available publications shows that the drugs indicated for the treatment of COVID-19 are not contraindicated for use by the nursing mother, making it possible to make treatment compatible with breastfeeding. In addition, other forms of treatment still under research are compatible in mothers who have clinical conditions to breastfeed or express breast milk. Thus, it is necessary to constantly update this topic due to the various researches involving new and numerous medications for the treatment of COVID-19. This article presents the drugs that can be used in the treatment of COVID-19 and its relationship with breastfeeding.

#### Palavras-chave:

Aleitamento Materno,  
Infecções por  
Coronavírus,  
Tratamento  
Farmacológico.

#### Resumo

Na recente pandemia do COVID-19 foi recomendado manter o aleitamento materno pelas mulheres com suspeita ou diagnóstico confirmado de infecção. Neste caso, devem ser adotados cuidados de biossegurança, para evitar a transmissão da doença para o recém-nascido. Revisões de publicações disponíveis mostram que os medicamentos indicados para o tratamento da COVID-19 não são contraindicados para uso pela nutriz, sendo possível compatibilizar o tratamento com o aleitamento. Também outras formas de tratamento, ainda sob pesquisa, são compatíveis em mães que apresentarem condições clínicas para amamentar ou extrair o leite materno. Deste modo, é necessária a constante atualização sobre esse tema, em virtude das diversas pesquisas envolvendo novos e numerosos medicamentos para o tratamento do COVID-19. Neste artigo são apresentados os medicamentos que podem ser utilizados no tratamento da COVID-19 e sua relação com a amamentação.

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## INTRODUCTION

The infection caused by the coronavirus 2019 (COVID-19), which started in the last few months, has become a pandemic with thousands of cases worldwide, including Brazil<sup>1</sup>. COVID-19 has also affected women who are breastfeeding, raising questions among the population and healthcare professionals about the risks of breastfeeding during this pandemic, and concerning the safety of medications that may be used to treat the disease.

### Breastfeeding by COVID-19-infected mothers

Researchers have not yet found the coronavirus 2019 (SARS-CoV-2) in breast milk, but specific antibodies against it have already been found in milk samples from infected mothers. So far, there is no evidence that the virus is transmitted through breastfeeding<sup>2,3</sup>. However, there can be droplet transmission through close contact during breastfeeding. Thus, mothers with confirmed COVID-19, or symptomatic mothers with suspected COVID-19, should take precautions to prevent transmission to the baby during breastfeeding, including assiduous hand hygiene and wearing a face mask<sup>3</sup>.

The World Health Organization<sup>4</sup>, the Brazilian Society of Pediatrics<sup>5</sup> and the Brazilian Federation of Gynecology and Obstetrics Associations<sup>6</sup> recommend maintaining breastfeeding for mothers with COVID-19 as long as the woman is able and willing to breastfeed. These mothers must adopt measures to reduce transmission of the virus through respiratory droplets during contact with the infant. The Academy of Breastfeeding Medicine adds that mothers who are away from their children due to hospitalization by COVID-19 and who wish to maintain breastfeeding should be encouraged to collect their milk, to maintain milk production<sup>7</sup>. In such cases, the mother should wash her hands thoroughly before pumping and wear a mask while pumping. If possible, a healthy person should carefully clean the collection equipment. In this context, the child can receive collected breast milk, through a caregiver, until the mother recovers, as long as the caregiver is healthy and follows hygiene precautions<sup>7</sup>.

### Use of medicines against COVID-19 by the nursing mother

The scientific literature has not yet shown an effective therapy against Covid-19, whether in the mild or severe forms of the disease. *In vitro* studies and clinical trials are ongoing with several drugs with potential for treatment<sup>8</sup>. In this study, we report on the evidence concerning safe drugs to treat COVID-19 during lactation. The authors do not intend to report on the efficacy of medications for the treatment of this disease. We present the drugs in alphabetical order.

The first systematic review on COVID-19 treatment was published in April 2020 and reported on a group of corticosteroids (methylprednisolone and dexamethasone)

as the most frequently used in China, followed by Lopinavir and Oseltamivir<sup>9</sup>. Other drugs under study to date include Favipiravir, Remdesivir, Ribavirin, Umifenovir, Interferon alfa, and Interferon beta, Nitazoxanide, Camostat, Tocilizumab<sup>10</sup> and Ivermectin<sup>11</sup>. Table 1 shows the drug safety classification for women to use during the lactation period.

**Table 1.** Drug safety classification for nursing mothers to treat COVID-19

Pharmacological Group	Drug	Classification to use during lactation
Antimalarial	Chloroquine	Safe
	Hydroxychloroquine	Safe
Antimicrobial (antibiotics)	Azithromycin	Safe
Antiparasitic	Ivermectin	Probably safe
	Nitazoxanide	Probably safe
Antiviral	Favipiravir	Not classified
	Lopinavir	Safe
	Oseltamivir	Safe
	Remdesivir	Safe
	Ribavirin	Safe
Corticosteroids	Dexamethasone	Probably Safe
	Methylprednisolone	Safe
Immunomodulators	Alpha interferon	Safe
	Interferon beta	Safe
	Tocilizumab	Safe

### Antimalarials - Chloroquine

Chloroquine is an antimalarial agent used for the prevention and treatment of malaria<sup>12</sup>. Studies have found very small amounts of chloroquine excreted in breast milk. Nursing mothers have reported no adverse effects on the infant after its use. However, the studies were carried out with the administration of weekly doses of this medication<sup>12</sup>. Few studies evaluated the daily maternal use of chloroquine during lactation. Chloroquine has a long clearance half-life (70 to 120 hours), but the peak serum concentration occurs between one and two hours and the relative dose in the infant is considered low (0.6% to 7.71%)<sup>12</sup>. A study showed that the amount of chloroquine excreted in breast milk is less than the recommended dose for use by infants<sup>13</sup>. The authors consider chloroquine compatible with breastfeeding<sup>12,13</sup>.

### - Hydroxychloroquine

Hydroxychloroquine is used to treat malaria and some immunological syndromes, such as rheumatoid arthritis and systemic lupus erythematosus<sup>12</sup>. Hydroxychloroquine has been

used more for patients with COVID-2019 than chloroquine, as it is considered safer and appears to have a more potent antiviral activity. In addition to the indication for the treatment of malaria, it is used in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Hale points out that hydroxychloroquine has a high distribution volume, suggesting very low levels in the breast milk. A recent study involving thirty-three women who had been using hydroxychloroquine for at least a year and were breastfeeding exclusively had the levels of hydroxychloroquine measured in milk over a 12-hour period. Dosages ranged from 200mg once every 2 days to 200mg twice a day. Follow-up for a period of one year, there was no ocular toxicity or abnormal growth in the infants<sup>14</sup>. Hydroxychloroquine is considered potentially safe for use during lactation<sup>12,14,15</sup>.

## Antimicrobials (antibiotics)

### - Azithromycin

Azithromycin is an antibiotic from the macrolides group that yields low levels in the breast milk, and is safe to use in infants. Thus, adverse effects are not expected to occur in infants after maternal use. One should monitor the infant for possible effects on the gastrointestinal flora, such as diarrhea and candidiasis. Unconfirmed epidemiological evidence warns that the risk of hypertrophic pyloric stenosis may be greater due to the maternal use of macrolide antibiotics, but studies have not found this association<sup>15</sup>. Recent publications consider azithromycin safe for use in lactation<sup>12,15,16</sup>.

## Antiparasitic

### - Ivermectin

Ivermectin is a drug indicated for the treatment of parasitic diseases such as onchocerciasis, filariasis and pediculosis. Limited data indicate that very little Ivermectin is excreted in breast milk after oral use. The concentration ingested by the infant is small, and one does not expect to have adverse effects<sup>15</sup>. A single study published with four women who received 150mcg/kg orally, found the concentration in milk 10 times lower than the dose administered. There are no reports of adverse effects on infants. Ivermectin is probably considered safe to use by nursing mothers<sup>12,15,16</sup>.

### - Nitazoxanide

Nitazoxanide is an antiparasitic agent with a broad spectrum of action against protozoa and helminths. It has pharmacokinetic properties, such as high binding to plasma proteins and short half-life clearance, which determine an insignificant concentration in breast milk<sup>16</sup>. A case study with a maternal dose of 500mg of nitazoxanide produced low levels of its active metabolite, tizoxanide in breast milk. The authors do not expect it to have adverse effects on infants. They recommend the use of an alternative medication until more data is published, especially during the breastfeeding

of a newborn or premature baby<sup>17</sup>. Experts consider the drug probably safe for use in lactation<sup>12,15</sup>.

## Antivirals

### - Favipiravir

Favipiravir is a new drug used in the experimental treatment of Ebola virus infection and, more recently, in patients with COVID-19. There is no information available on the use of favipiravir during breast-feeding or on its excretion in breast milk. Favipiravir has a low molecular weight, and 60% of the absorbed concentration is transported bound to plasma proteins. Therefore, it is expected to be found in milk and absorbed by the infant, probably in small quantities. In clinical trials, favipiravir was well tolerated, but it elevated liver enzymes, caused gastrointestinal symptoms and increased serum uric acid. One should monitor these parameters in infants when using favipiravir in nursing mothers<sup>15</sup>.

### - Lopinavir

It is an HIV protease inhibitor antiviral agent, used in combination with ritonavir<sup>12,16</sup>. A study that evaluated the use of lopinavir by 60 lactating mothers in treatment of HIV infection did not find the presence of the drug in breast milk samples<sup>18</sup>. Other studies revealed a small concentration of lopinavir in breast milk samples<sup>19,20,21</sup>. The low molecular weight and high binding to plasma proteins may justify these findings<sup>16</sup>. A study evaluated the serum concentration of lopinavir in infants who received the drug excreted via breast milk. The authors reported that infants receive insignificant concentrations of lopinavir through breastfeeding<sup>22</sup>, and the studies did not find adverse effects in infants after maternal use of lopinavir. Women with HIV<sup>12</sup> base studies that recommend avoiding its use during lactation on the contraindication of breastfeeding.

### - Oseltamivir

Oseltamivir is an antiviral drug indicated for the prevention and treatment of uncomplicated acute forms of influenza A and B viruses, being an inhibitor of viral neuramidase that blocks the viral spread and release from infected cells<sup>12</sup>. A study evaluated the excretion of oseltamivir in the milk of seven women and found concentrations considered extremely low<sup>23</sup>. Experts state that adverse effects are not expected to occur in breastfed infants after maternal use of oseltamivir, and consider the drug safe for use in lactation<sup>12,15,16</sup>. Nursing mothers by the Center of Disease Control (CDC)<sup>24</sup> recently approved Oseltamivir for use.

### - Remdesivir

Remdesivir is a nucleotide analog drug that inhibits viral RNA polymerase<sup>16</sup>. To date, there are no papers on the excretion of remdesivir in breast milk. There is no pharmacokinetic data corroborating its excretion to the milk

compartment. However, its moderately high molecular weight can make it difficult for it to pass into breast milk<sup>16</sup>. Remdesivir has low absorption by the gastrointestinal tract; a fact that makes it unlikely that the infant would absorb it via breast milk<sup>15</sup>. One study reported that there was no adverse effect in premature newborns with 19 days of life infected with the Ebola virus who received remdesivir intravenously for 12 days. The child was followed for 12 months and showed normal growth and development<sup>25</sup>. Remdesivir is classified as bearing low risk to use during lactation<sup>16</sup>.

#### **- Ribavirin**

Ribavirin is a synthetic nucleoside used as an antiviral agent, especially in infections caused by the respiratory syncytial virus in infants<sup>12</sup>. To date, there is no published data on its excretion in breast milk. Its large distribution volume makes it unlikely that significant quantities will pass into the milk. Its low oral bioavailability limits the passage to the infant's plasma from ingested milk, except in premature milk and in the immediate neonatal period, for which there may be an increased intestinal permeability<sup>16</sup>. Since it is used as a treatment in infants and its pharmacokinetic data is favorable, it must be considered compatible with breastfeeding for short-term exposures; however, to be used with caution in long-term treatments<sup>16</sup>. A relevant publication that considers ribavirin as "possibly dangerous" for use in lactation justifies the classification only for its use for a period of 6 to 12 months in patients undergoing treatment for hepatitis C. The author states that acute exposure of a breastfed infant produces minimal side effects<sup>12</sup>.

#### **Corticosteroids**

##### **- Dexamethasone**

Dexamethasone is an anti-inflammatory drug from the group of corticosteroids with prolonged action. There is no published data on the transfer of dexamethasone into breast milk; however, it is estimated to be low. Infants use dexamethasone without reports of adverse effects for a short period<sup>12</sup>. Thus, it is classified as probably safe for use during lactation<sup>12,16</sup>. There has been a report of a reduction in the release of prolactin after the administration of dexamethasone, with a risk of reduced milk production, especially in the first weeks after delivery<sup>26</sup>.

##### **- Methylprednisolone**

Methylprednisolone is a corticosteroid drug administered intravenously to treat various inflammatory diseases. Several studies have evaluated the use of methylprednisolone during lactation. Low concentrations of the drug were found in breast milk, with no adverse effects reported in breastfed infants. One study revealed that intravenous doses of 1mg of dexamethasone administered to the nursing mother produced serum concentrations below the daily cortisol production of an exclusive breastfeeding

infant. It also showed that there was no accumulation of the drug in breast milk after 3 consecutive daily doses<sup>27</sup>. Some experts recommend waiting 2 to 4 hours for breastfeeding after intravenous administration of high doses of dexamethasone in order to minimize the infant's exposure to the drug<sup>16</sup>. Respected entities such as the World Health Organization and the American Academy of Pediatrics consider dexamethasone compatible with breastfeeding<sup>28,29</sup>.

#### **Immunomodulators**

##### **- Alpha interferon**

Alpha interferon is a cytokine with antiviral, antiproliferative and immunomodulating properties, produced by leukocytes and lymphoblasts obtained by recombinant DNA engineering; indicated for the treatment of chronic hepatitis B and C and some neoplasms, such as leukemia<sup>16</sup>. It has a high molecular weight<sup>12</sup>, low absorption by the digestive tract, low levels in breast milk, and adverse effects on the infant are unlikely to occur after the maternal use of this drug<sup>12,15</sup>. Alpha interferon is compatible with breastfeeding<sup>12,16</sup>.

##### **- Interferon beta**

Beta Interferon is a cytokine with antiviral, antiproliferative and immunomodulatory properties, being produced by fibroblasts and obtained by recombinant DNA engineering. It is used in the treatment of multiple sclerosis<sup>16</sup>. Due to its high molecular weight, the transfer of interferons in human milk is limited, although we know that some interferons, such as gamma interferon, are secreted and contribute to the antiviral effect of human milk. The transfer of Interferon beta 1B into breast milk is probably null<sup>12</sup>. This drug is usually indicated in high doses for infants with immune thrombocytopenic purpura, being considered safe. Experts consider the use of Interferon beta compatible with breastfeeding<sup>12,16,29</sup>.

##### **- Tocilizumab**

Tocilizumab is a human monoclonal antibody that inhibits the interleukin 6 receptor and is indicated for the treatment of rheumatoid arthritis, juvenile arthritis and Castleman's disease<sup>16</sup>. A recent study showed a low concentration of tocilizumab in breast milk, probably due to its high molecular weight<sup>30</sup>. Experts warn of the greater possibility of intestinal absorption by newborns and premature infants, but consider the drug safe for use during lactation.<sup>12,15,16</sup>

#### **FINAL CONSIDERATIONS**

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The recent COVID-19 pandemic brought several challenges to the scientific community, among them the need for constant updating on various topics such as caring for the nursing mother. There is consensus among the various healthcare authorities on the maintenance of breastfeeding by women with

suspected or diagnosed COVID-19, adopting biosafety care to prevent the transmission of the disease to their infants. Nursing mothers do not contraindicate the drugs currently researched and indicated for the treatment of COVID-19 for use, and it is possible to make treatment compatible with breastfeeding for mothers who have clinical conditions to breastfeed or collect breast milk. Thus, it is necessary to constantly update this topic due to the various studies involving new and numerous medications for the treatment of COVID-19.

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