

# Pharmacotherapy of COVID-19: Considerations for Pregnancy and Breastfeeding

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## ABSTRACT

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a chief concern of the international community. As of May 2021, more than 150 million cases and 3.2 million deaths have been recorded. Considering the early struggle in treating COVID-19 patients, the researchers and clinicians have decided to try the previously available drugs according to their mechanisms of action. This article aims to review the potential drugs for COVID-19 patients during pregnancy and breastfeeding and their safety. PubMed and Scopus databases and Google Scholar engine were searched with the proper combination of the free keywords and MeSH Terms of COVID-19, SARS-CoV-2, Pregnancy, Breastfeeding, Treatment, Pharmacotherapy, Drug Therapy, and Drug Safety. All relevant clinical studies published until the end of 2020 were considered in this review. Many antivirals, antibiotics, antiparasitics, and antipyretics have been proposed, but most of them are not registered for COVID-19 or have demonstrated little effect on the disease. Since there is still a long way to find an effective drug for the treatment of COVID-19, prevention is currently the most effective way. Also, prescribing drugs to these two groups of patients should be done according to the safety recommendations.

**Keywords:** Angiotensin converting enzyme 2, Breastfeeding, Drug therapy, Pregnancy, Severe acute respiratory syndrome coronavirus 2



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## Introduction

On January 7<sup>th</sup>, 2020, the Chinese Center for Disease Control and Prevention (China CDC) identified a new coronavirus, later called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by World Health Organization (WHO) (1). The virus rapidly spread globally and became a chief international concern, with more than 150 million confirmed cases and 3.2 million reported deaths until May 2021 (2). From the first days, clinicians and researchers worldwide attempted to find effective drugs to treat coronavirus disease 2019 (COVID-19), but no drug was approved as a definitive treatment. In this situation, left with no other choice than to use the formerly used drugs, most current clinical approaches consist of repurposing the previously available drugs that are expected to act as potential anti-COVID-19 agents, based on their underlying mechanisms of action.

Besides the general considerations regarding the drug-to-drug interactions, as the pregnant and infants are among the most vulnerable groups, and the behavior of the virus among pregnant women and infants is still ambiguous (3), we aim to review the safety of

using the repurposed medications during the pregnancy and breastfeeding in this study.

## Materials and Methods

During this review, PubMed and Scopus databases and Google Scholar engine were searched with the free keywords and MeSH Terms of COVID-19, SARS-CoV-2, Pregnancy, Breastfeeding, Treatment, Pharmacotherapy, Drug Therapy, and Drug Safety, for articles published until the end of 2020. All relevant clinical studies were considered in this review.

## Results & Discussion

The proposed medications for the treatment of COVID-19 infection in pregnant or breastfeeding patients are identified as below:

### Antiparasitics

Chloroquine and Hydroxychloroquine are FDA-approved agents against malaria. The immunomodulatory effects and the impact of inhibiting the virus-

cell fusion have turned these drugs into prodigious hopes for COVID-19 treatment (4). Although Chloroquine and Hydroxychloroquine can pass through the placental barrier, studies have shown that no danger threatens the fetus (5). Despite the little excretion of Chloroquine into the milk, the American Academy of Pediatrics considers it compatible with breastfeeding, leaving no concern around the usage of Chloroquine and Hydroxychloroquine during breastfeeding (6). Recently, several studies, including the WHO Solidarity clinical trial, have reported that Chloroquine and Hydroxychloroquine have low efficacy in treating COVID-19 patients, which has led to omitting these drugs from the COVID-19 treatment protocols in most of the countries (7).

#### Antibiotics

As a broad-spectrum antibiotic in respiratory infections, Azithromycin is another drug that has been investigated as a choice of pharmacotherapy for SARS-CoV-2 infection. With a history of proven antiviral activity against Ebola, Zika, and Influenza A virus subtype H1N1, some researchers believe that comparing to Chloroquine and Hydroxychloroquine, Azithromycin could possibly be a better choice (8). Studies have shown that the combination therapy of Hydroxychloroquine and Azithromycin was influential in the treatment of COVID-19 patients (9). Nevertheless, a recent systematic review of the literature found no efficacy for this drug in COVID-19 patients (10). Also, the results of COALITION I and II clinical trials in Brazil found no improvement in clinical outcomes of the 447 enrolled COVID-19 patients (11). Today, the Infectious Diseases Society of America (IDSA) guideline recommends against the combination therapy of Azithromycin and Hydroxychloroquine because of reported increase in risk of QT prolongation, but this recommendation did not address the use of this drug against secondary bacterial pneumonia in COVID-19 patients (12). Azithromycin excretes into human milk, but there are limited data available in both human and animal studies regarding the harmful effects of Azithromycin on the fetus or infant. However, in case of clear need, Azithromycin can be used during pregnancy and breastfeeding (13).

#### Antivirals

A failed Ebola drug, Remdesivir, acts well in shortening the recovery time of COVID-19 patients. The FDA authorized this drug for emergency use on October 22<sup>nd</sup>, 2020. Although on November 20<sup>th</sup>, WHO recommended against Remdesivir (14), on November 25<sup>th</sup>, FDA declared that “*The approval of Remdesivir for the treatment of patients hospitalized with COVID-19 met the legal and scientific standard*” in a published statement (15). The safety of Remdesivir usage during pregnancy and breastfeeding is still under investigation. However, its usage during pregnancy is only allowed after harm-benefit assessment for each patient. A case report of successful management of pregnant women in the third trimester with Remdesivir recommended including pregnant women in clinical trials

(16). Nevertheless, almost all clinical trials have excluded pregnant and breastfeeding women from their sample (17). The results of a study conducted on pregnant women who were treated with Remdesivir showed a high recovery rate with a low rate of serious adverse events (18). In this study, 93% of patients were recovered, and 90% were discharged, and the rate of serious adverse events was 16%. Only the severe cases of COVID-19 had the indication for Remdesivir injection. In this situation, it is most probably not to breastfeed their infants (19).

Lopinavir/Ritonavir as a licensed treatment for HIV had been recommended for COVID-19 treatment in many countries. Contrary to clinicians' hope, previous studies have shown no significant improvement in the clinical conditions of COVID-19 patients (7). While the previous studies have shown no concern regarding the standard-dose prescription of this drug during pregnancy, the use of the oral solution is contraindicated during pregnancy, as it contains alcohol and propylene glycol (20). Most of the available guidelines recommend HIV-infected mothers not to breastfeed their infants, so there is limited data about this drug's safety during breastfeeding. Despite the little excretion in breastmilk, there is no report of adverse events caused by using Lopinavir/Ritonavir in infants (21). Also, a recent systematic review has reported low placental transfer of Lopinavir/Ritonavir (22).

Favipiravir is another potential antiviral agent against COVID-19. Even though there are reports of its efficacy against mild and moderate cases of COVID-19, numerous contrary studies are available (23). A recent systematic review has reported Favipiravir as an effective drug in improving the clinical condition of COVID-19 patients (24). Although Favipiravir has received approval for emergency use in many countries, further studies are still needed to substantiate the effective role of this drug (25). Thirty-one clinical trials have already been registered, which will provide more reliable evidence of using this drug against COVID-19. Favipiravir has shown teratogenic effects in several species and should not be prescribed for pregnant women (26). There is no information about its excretion into milk and safety for the newborn (21), but according to animal studies, breastfeeding is contraindicated during the treatment course of Favipiravir (26).

Another proposed agent for COVID-19 therapy is Interferon beta-1a (IFb1a), an immunomodulatory agent with antiviral effects used in the treatment of multiple sclerosis (MS). A clinical trial of 20 patients recommended adding IFb1a to the treatment regimen of infected patients (27). Also, a controlled trial of safety and efficacy of inhaled nebulized Interferon beta-1a found it effective in treating COVID-19 (28), in contrast with the results of the WHO Solidarity study (29). Notably, the pregnant and lactating women were excluded from the studies. Animal studies showed no teratogenic effects of IFb1a. Even though the usage of this agent during pregnancy was contraindicated, on

April 4<sup>th</sup>, 2020, FDA approved that the drug does not have deleterious effects on pregnancy and pregnancy-related outcomes; however, most of the ongoing clinical trials excluded pregnant and lactating women from their study (30). Since the levels of interferon beta-1a excretion in human milk are negligible, no adverse infant effects had been reported in women who have breastfed while taking IFb1a (19).

### Baricitinib

Baricitinib is a long-term medication against rheumatoid arthritis, which has shown potential for COVID-19 treatment and received the FDA approval for emergency use combined with Remdesivir (31). This approval was primarily based on the results of a large randomized controlled trial of 1033 participants, which showed that compared with the Remdesivir monotherapy, Remdesivir and Baricitinib has better efficacy in improving the clinical status of the COVID-19 patients (32). Although a recent case report stated the positive outcomes of using Baricitinib in the first 17 weeks of pregnancy (33), available clinical and experimental studies recommend against prescribing Baricitinib during pregnancy and breastfeeding.

### Antipyretics

Fever is the most common symptom of COVID-19 (34). Defects of craniofacial development, teeth, and heart problems are also commonly observed (35). Even mild exposure during the preimplantation period could result in abortion (36). In order to prevent the complications of fever, Acetaminophen is a safe choice for the pregnant, but the use of Ibuprofen is a point of controversy. Studies claim that Ibuprofen may exacerbate the patients' condition by increasing the amount of angiotensin-converting enzyme 2 (ACE2) (37).

On the other hand, studies claim to treat critically ill patients by blocking the inflammatory mediator interleukin-6 with this drug (38). Finally, on March 19<sup>th</sup>, the World Health Organization (WHO) stated that there is not enough evidence against the use of Ibuprofen, and they do not advise against it. Generally, pregnant women are recommended to avoid taking Ibuprofen, especially during the third trimester, since it could lead to premature closure of the fetal ductus arteriosus and develop heart problems in the fetus. Hence, physicians should weigh the benefits and harms before prescribing Ibuprofen. As a preferred choice of analgesic during lactation, the excretion of Ibuprofen into the breast milk is extremely low. It should be noted that NIH advises avoiding both Ibuprofen and Acetaminophen during the first trimester of the pregnancy.

### Conclusion

Prescribing medication for pregnant or lactating patients infected with SARS-CoV-2 is challenging. A summary of drug safety for pregnancy and lactation is presented in Table 1. The results of the solidarity clinical trial for COVID-19 treatments launched by WHO found little or no effect for Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon. More than mentioned drugs, novel ribonucleoside analog (NHC, EIDD-1931) was promising in recent studies. Preclinical studies found it a potential therapy against SARS-CoV-2, MERS-CoV, and SARS-CoV, but we still need clinical studies to confirm its safety and efficacy. It seems that there is still a long way to find an effective drug for the treatment of COVID-19; therefore, preventing infection is the most effective way to cross through this pandemic.

**Table 1.** Safety categories of potential COVID-19 drugs during pregnancy and excreted into milk

Drug	Australian Drug pregnancy Categories	United States FDA pregnancy category	Excretion into human milk
Acetaminophen	A	Not Assigned.	Yes
Azithromycin	B1	B	Yes
Baricitinib	D	Not formally assigned.	Yes <sup>2</sup>
Chloroquine	A/D <sup>1</sup>	Not formally assigned.	Small amounts
Favipiravir	-	-	-
Hydroxychloroquine	D	Not formally assigned.	-
Ibuprofen	C	C	Small amounts
Interferon-beta-1a	D	C	-
Lopinavir/Ritonavir	B3	Not assigned.	Yes
Remdesivir	B2	Not assigned.	Yes <sup>2</sup>

<sup>1</sup>For malaria treatment: D and for Malaria prophylaxis: A.<sup>2</sup>Based on animal studies.

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## Ethical Permission

Not applicable.

## Authors Contribution

Conceptualization, A.N., and MS.H.; data curation, A.N., and S.S.; writing—original draft preparation,

A.N., and S.S.; writing—review and editing, MS.H.; project administration, MS.H. All authors have read and agreed to the published version of the manuscript.

## Conflict of Interest

None declared by Authors.

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