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## REVIEW ARTICLE

# Safety profile of treatments administered in COVID 19 infection in pregnant women



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### KEYWORDS

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**Abstract** SARS-CoV-2 infection has unexpectedly arrived in our society. In pregnant women, the situation has been similar to general population. Some drugs have been used empirically, and obstetricians have to consider whether the same treatments used in the general population were valid for pregnant women with severe disease, according to their safety profile for both the mother and the fetus. There has been a wide experience with the use of hydroxychloroquine and lopinavir/ritonavir in pregnant women. Tocilizumab and interferon beta could be used if benefits exceed risks. There is no experience using remdesivir in pregnancy.

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### PALABRAS CLAVE

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### Perfil de seguridad del tratamiento específico de la infección por COVID-19 en el embarazo

**Resumen** La infección por SARS-CoV-2 ha llegado a nuestra sociedad de forma inesperada. En las mujeres embarazadas, la situación ha sido similar a la de la población general. Algunos fármacos se han utilizado de forma empírica y los obstetras deben considerar si los mismos tratamientos utilizados en la población general son válidos para mujeres embarazadas con enfermedad grave, de acuerdo con su perfil de seguridad tanto para la madre como para el feto. Existe una amplia experiencia con el uso de hidroxycloroquina y lopinavir/ritonavir en mujeres embarazadas. Se podrían usar tocilizumab e interferón beta si los beneficios superan los riesgos. No hay experiencia en el embarazo con remdesivir.

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## Introduction

SARS-CoV-2 infection has come to our society unexpectedly. Currently there is still little knowledge of its behavior and progression in infected patients. The first cases were described in China in late December 2019.<sup>1</sup> While an effective vaccine or specific antiviral treatment is found, the rapid increase in the rate of serious infections and deaths has urged the scientific community to identify and use different drug options, sometimes on an experimental basis, in order to avoid worsening of infected patients and minimize their symptoms.<sup>2</sup>

It is known that pregnancy predisposes women to respiratory complications of viral infection due to the physiological changes in their immune and cardiopulmonary system.<sup>3,4</sup> Infection with SARS-CoV and MERS-CoV can be responsible for severe complications during pregnancy, including the need for endotracheal intubation, admission to an intensive care unit (ICU), renal failure and death.<sup>4,5</sup> However, coronavirus disease (COVID 19) in pregnant women, have been similar to the general population in terms of contagiousness and affectation. The majority of pregnant women have mild disease (92%).<sup>6</sup>

Early data regarding pregnancy outcomes in COVID 19 is hopeful because vertical transmission and neonatal infection are rare.<sup>7</sup> Despite of this, obstetricians have to consider whether the same treatments used in the general population were valid for pregnant women with severe disease according to their safety profile for both the mother and the fetus. Because of pregnant women are usually excluded in therapeutic drugs and vaccine trials, the decision about choosing the best drug when it is needed, in terms of helpful and maternal-fetal security, are based on the experience of using these "anti COVID 19 drugs" for other medical indications in pregnancy.<sup>8,9</sup>

The objective is to review the experience using this drug in pregnancy, because they will inevitably receive therapies whenever they seem effective in nonpregnant patients and even under compassionate use.<sup>10</sup>

## Drugs used for COVID 19 disease

### Hydroxychloroquin and chloroquin

Hydroxychloroquin is an antimalarial agent with anti-inflammatory and immunomodulatory activities and it seems that it helps by inhibiting the exacerbation of pneumonia, improve lung imaging findings, promotes a virus-negative conversion and it shortens the duration of the COVID 19.<sup>8</sup>

It is safe during pregnancy at doses of 200mg once or twice a day<sup>10</sup> and it is the medication of choice in women who need to maintain treatment during pregnancy for rheumatic diseases such as erythematosus systemic lupus (SLE), rheumatoid arthritis (RA) or Sjögren Syndrome (SS).<sup>11,12</sup> There is extensive good experience of use in these cases and pregnancy outcomes, in terms of miscarriages and fetal malformations, are similar between exposed pregnant women and not exposed to the drug.<sup>11,13</sup>

Chloroquine is an antimalarial drug and in vitro reduces coronavirus replication interfering with the angiotensin converting enzyme 2 (ACE2) receptor in the SARS-CoV-2.<sup>14</sup>

Chloroquine crosses the placenta but no adverse pregnancy outcomes have been reported in exposed pregnant women.<sup>10,15</sup>

### Lopinavir/ritonavir

It is an antiviral combination that belongs to the group of the protease inhibitors (PI). It is used in combination with two analog reverse transcriptase inhibitors (ARTI), in the so-called High Activity Antiretroviral Therapy (HAART).<sup>16</sup> Lopinavir is a PI and ritonavir is an inhibitor of cytochrome p450 and is used as a booster to obtain therapeutic plasma concentrations.<sup>10</sup>

It has in vitro and in vivo efficiency against SARS-CoV-1 and MERS infections, so they were considered as a treatment option for SARS-CoV-2 infection,<sup>17</sup> but first randomized trial reported no significant benefits.<sup>18</sup>

We have extensive experience of its use in pregnant women with HIV infection. This pharmacological combination has a minimal transplacental passage. Recommended dosage is twice a day (it is not recommended to use them only once a day) and it will be considered to increase the dose in the third trimester if needed.<sup>16</sup> Pregnancy outcomes reported in women using lopinavir/ritonavir is similar to HIV women that do not taking it.<sup>19</sup>

### Immunomodulators: tocilizumab

Tocilizumab (TCZ) is a recombinant and humanized IgG monoclonal antibody against IL-6. Exposure to the drug in the periconceptional period and/or the first few weeks of gestation does not appear to increase the risk of birth defects. A previous study has reported an increased risk of abortion, but the patients had other concomitant treatments such as methotrexate, so this outcome cannot be directly related to exposure to TCZ.<sup>20</sup>

The use of tocilizumab is limited to severe COVID 19 infection. These patients have a cytokine storm which is a hyperinflammatory syndrome that lead to multiorgan failure. IL-6 participates in the SARS-CoV-2 cytokine storm, that is the reason this drug has been considered as a treatment for coronavirus disease.<sup>10,21</sup>

There is previous experience of use in pregnant women with rheumatic disease. Tocilizumab crosses the placental barrier and it is found in blood cord samples (89% of maternal plasma dosage).<sup>22</sup> Although in some studies it has been reported an increased risk of maternal and fetal complications such as a preterm delivery (31.2%) and spontaneous abortions (21.7%). However, a direct relationship cannot be established with the use of the drug since it is abandoned in most cases at the beginning of gestation and co-medication, included methotrexate, was used by the prospectively ascertain cases.<sup>20,23</sup> Those pregnant women who had to maintain or restart the drug due to clinical deterioration, had healthy newborns.<sup>23</sup>

The expert recommendations are that if the benefits exceed the potential risk, the drug can be maintained along the pregnancy or it can be reintroduced. Although the data are scarce, this information may be useful in giving information to patients and doctors to make decisions.<sup>20,23</sup>

Other antiinterleukin inhibitors (anti-IL-1), canakinumab and anakinra, are under investigation.<sup>10</sup>

Infliximab is an anti-TNF drug, used for Chron's disease also in pregnant women with wide experience.<sup>24</sup> It crosses the placenta in second and third trimesters, but no increased risk of congenital malformations has been reported. If necessary for control the disease it can be maintained until the end of the pregnancy.<sup>24</sup> In COVID 19 context, is under consideration for treating severe pneumonia.<sup>10</sup>

Colchicine is an anti-inflammatory drug that could reduce cytokine storm and inflammatory cascade activation in severe COVID 19 disease. It is used in Behçet's disease pregnant women and other autoimmune diseases (psoriasis, familiar Mediterranean fever. . .) with no increased risk of congenital malformations.<sup>25</sup> To date, no effectiveness has been reported for treating SARS-CoV-2 infection.<sup>10</sup>

Other immunosuppressive drugs, such as, baricitinib and leflunomide are valued for COVID 19 disease but nowadays they are not recommended in pregnancy. Baricitinib, a Janus Kinase (JAK) inhibitor has very few safety data in pregnant women and leflunomide, an immunosuppressor, is teratogenic in animal models.<sup>10</sup>

### Interferon beta

This drug is a cytokine from the interferon family with antiviral, antiproliferative and immunomodulatory effects.<sup>10</sup> There is experience on its use in pregnant women with multiple sclerosis (MS) to treat recurrent-relapsing forms.<sup>26</sup>

Interferon beta has been proposed as immunomodulatory treatment for control the massive inflammation in severe COVID 19.<sup>10</sup>

Its use in pregnancy is not approved in the technical sheet, although there is no evidence of an increased risk of abortions or congenital malformations in women with MS exposed to interferon beta. Since the risk of outbreak in these patients decreases during pregnancy, it does not seem appropriate to keep the medication throughout it, however, if necessary due to the presence of significant activity, it can be administered throughout the pregnancy and it has not been seen fetal harm associated with the use of this drug. There are conflicting data regarding the risk of restricted intrauterine growth and premature delivery.<sup>27,28</sup>

Other drug used in the field of MS and also under investigation as a COVID 19 therapy is fingolimod, an immune modulator which prevents autoimmune reaction. There are safety data concerning risk of congenital malformations when used in MS pregnant women compared with general population.<sup>29</sup>

### Remdesivir

Remdesivir is a nucleotide analog inhibitor of RNA polymerase. It has been used in the treatment of Ebola virus infection and experimentally in COVID 19 infection. There is no experience of use in pregnancy.<sup>10,30</sup>

Six patients with positive pregnancy test were treated with remdesivir in a clinical trial for treatment of Ebola virus infection, without subsequently referring to perinatal results in these patients in the event of non-death and continued pregnancy.<sup>31</sup> Other few published works on this

matter do not refer to the use of the drug specifically in pregnant women. Considering its small molecular weight and its high protein-binding, it is expected that remdesivir could cross the placenta.<sup>10</sup>

In the case of pregnant women infected with SARS-CoV-2 with severe symptoms or disease progression with the need of mechanic ventilation,<sup>2</sup> probably the use of remdesivir will be prioritized to avoid maternal worsening.

Other antivirals, such as oseltamivir has been used for influenza infection, also in pregnant women, with no increased risk of fetal malformations or other pregnancy complications when it is used.<sup>32</sup> Favirapivir is another antiviral drug that is under investigation for treating COVID 19 disease in clinical trials.<sup>10</sup> And some drugs are under consideration for treating SARS-CoV-2 but not results have been reported yet (ribavirin, darunavir, nelfinavir, clevudine. . .).<sup>10</sup>

### Antiinfective drugs: azithromycin

It is a macrolid antibiotic and is used in pregnancy and no increased risk of major congenital malformations have been reported.<sup>10,33</sup> For COVID 19 disease it seems that the combination of azithromycin with hydroxychloroquine is more effective than this last one alone.<sup>34</sup>

Other antiinfective drugs are under investigation in clinical trials for treating COVID-19 such as ivermectin and nitazoxinide. They have been used for parasite infections and there is insufficient safety data for using in pregnancy.<sup>10</sup>

### Other medications

Drugs that modify the renin-angiotensin-aldosterone system are considered for treating COVID 19 disease (losartan, telmisartan. . .). This type of medications can damage fetal kidney, leading to renal failure. They may also affect placental functions increasing the risk of growth retardation in these fetuses. For all this reason, they are not recommended in pregnancy.<sup>10,35,36</sup>

Also contraindicated in pregnancy but under investigation for COVID 19 disease are drugs such as bevacizumab (antivascular endothelial growth factor antibody), thalidomide (antitumoral agent).<sup>10</sup>

Transfusion of immunoglobulins from patients who have recovered from the disease have been approved to treat critically ill patients and is also been evaluated in clinical trials.<sup>10</sup> Immunoglobulin G (IgG) can cross the placenta, mostly in second and third trimester, and they are very important preventing neonatal infections as a passive immunization.

### Other used drugs not directly against COVID 19 disease

#### Glucocorticoids

Lung maturation with corticosteroids should be managed according to the usual doses and recommendations of the obstetric and gynecology societies since the use of non-fluorinated corticosteroids does not ensure lung maturation.<sup>37</sup>

Prednisone is inactivated by 11 $\beta$ -hydroxysteroid dehydrogenase in the placenta and converts it into the relatively inactive forms, leaving no more than 10% of the active drug to reach the fetus.<sup>10,38</sup> Fluorinated glucocorticoids (betamethasone and dexamethasone) are considerably less well metabolized by the placenta. This is the reason they are used for treat the fetus.<sup>39</sup>

Methylprednisolone and dexamethasone are being studied in prospective controlled trials for the management of SARS-Cov-2 infection.<sup>10</sup>

### Low molecular weight heparine

Pregnancy and postpartum period are considered risk factors for venous thromboembolic disease (VTE) because of all physiological changes that occurs in coagulation status, cava venous compression by the uterus and tissue damage. VTE risk stratification is required to determine which women warrant pharmacological thromboprophylaxis.<sup>40</sup> Low molecular weight heparine (LMWH) is the preferred medication for the treatment and prevention of VTE in pregnancy.<sup>41</sup>

Patients with severe COVID 19 disease have several risk factors for VTE (immobilization, respiratory failure, mechanical ventilation and central venous catheter use).<sup>42</sup> Also, VTE is more frequent in patients with pneumonia caused by pneumococcal or influenza infection.<sup>43</sup>

The coexistence, therefore, of a COVID 19 infection in a pregnant woman makes it necessary the VTE evaluation for identify patients at high risk for VTE and provides them appropriate thromboprophylaxis.<sup>43,44</sup>

### Discussion

SARS-CoV-2 infection has revolutionized not only doctors and patients but the entire scientific community. Multiple papers have appeared in this regard that have tried to help the management of this unknown disease. Pregnant women have not been less and have also suffered COVID 19 disease, so we have seen the need to use empirical treatments for the disease and without data or with little safety data on its use in pregnancy.<sup>1</sup>

Almost a year after the onset of the pandemic, we are acquiring some experience of use but there is still a long way to go since as on other occasions with other drugs, pregnant women are a group that are not included in clinical trials and that the use of drugs used to be out of label.

Luckily, we are gaining safety in the use of certain drugs such as HIV protease inhibitors (lopinavir/ritonavir), interferon, hydroxychloroquine, azithromycin, colchicine, steroids, oseltamivir and some monoclonal antibodies (infliximab and possibly tocilizumab). In the other hand, there are known forbidden drugs because of their teratogenicity (thalidomide and renin-angiotensin system blockers).

We also consider a third group of drugs, that one with insufficient safety pregnancy data, for example some IL-6 or IL-1 inhibitors, antivirals (remdesivir, favipir...), ivermectin... but absence of data does not imply evidence of harm. So it is important to inform the pregnant women all the therapeutic options and agree with obstetricians and

medical specialist the best drug in each case, taking into account the safety for the fetus but also for the mother.

### Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

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