




# Corticosteroids Use in Pregnant Women with COVID-19: Recommendations from Available Evidence

This article was published in the following Dove Press journal:  
*Journal of Multidisciplinary Healthcare*

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**Abstract:** Pregnant women experience immune system changes to accommodate and tolerate the growing foetus, these changes also increase their susceptibility to viral infections such as SARS-COV-2. COVID-19 in pregnancy increases the likelihood of hospital admission and intensive care compared to non-pregnant women. Early administration of low-dose corticosteroids to patients with acute respiratory distress syndrome can reduce all-cause mortality among such patients. However, during pregnancy, prolonged use of corticosteroids that readily cross the placenta like dexamethasone can negatively impact both the mother and foetus. Evidence is thus needed on the choice, timing, and duration for corticosteroids use among pregnant women with COVID-19. This article aims to provide evidence on corticosteroid use in pregnant women with COVID-19. The RECOVERY trial deduced that low-dose dexamethasone (6 milligrams) reduced mortality by up to one-third among COVID-19 patients on mechanical ventilation and one-fifth among those who received supplemental oxygen. Pregnant women in this trial received either oral prednisolone or intravenous hydrocortisone. Based on the RECOVERY trial findings, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends that pregnant women with moderate-to-severe COVID-19 receive oral prednisolone or intravenous hydrocortisone. However, currently, the World Health Organisation (WHO) does not explicitly specify which corticosteroid to use among pregnant women with moderate-to-severe COVID-19. We also note that there are no published articles on corticosteroid use among pregnant women with severe COVID-19 in Africa.

**Keywords:** COVID-19, corticosteroids, pregnant-women, prednisolone, preterm birth

## Background

Globally, health systems have been immensely strained by COVID-19 cases since it was declared a global pandemic by the World Health Organisation on 11 March 2020.<sup>1,2</sup> With more than 100 million Covid-19 cases and 2.4 million deaths worldwide, evidence on the effect of COVID-19 in pregnancy is still scanty.<sup>3,4</sup> However, the available data elucidates that there may or may not be a different disease progression pattern at the various stages of pregnancy.<sup>5</sup> Maternal changes in the immunity (immune modulation) to accommodate and tolerate the growing foetus is known to predispose pregnant women to the wrath of viral infections.<sup>4</sup> Pregnancy exacerbates the morbidity of COVID-19, with the effect potentiating as the pregnancy nears term.<sup>4,6,7</sup> Pregnancy increases the probability of hospital admission and intensive care.<sup>6,8</sup> There is, however, no difference in the risk of dying from COVID-19 between pregnant and non-pregnant women.<sup>4</sup>

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There is still elusive evidence about the incidence, transmission, and effects of COVID-19 among pregnant women and their fetuses.<sup>4</sup> Nevertheless, several studies have thrown some light on how the disease affects this vulnerable population. For instance, when admitted for COVID-19, pregnant women are likely to have comorbidities, for example, asthma, hypertension, type 2 diabetes, obesity, and autoimmune diseases, just like their non-pregnant counterparts.<sup>7,8</sup> Early preliminary reports showed that the risk of infection was more apparent as the pregnancy neared term, and it still holds.<sup>4,9</sup> Such studies also indicated that many pregnant women contracted COVID-19 during the third trimesters, and the majority had prodromal symptoms.<sup>4,9</sup> However, as the pandemic has progressed, more women have presented with COVID-19 as early as the first trimester. Most pregnant women with COVID-19 are asymptomatic; many others have mild symptoms, from cough, myalgia, headache, to fevers, loss of taste or smell senses.<sup>4,10–12</sup> A hospital analysis in the UK deduced that pregnant women with COVID-19 at 20 weeks' gestation and beyond are five times more likely to be admitted to intensive care units than those below 20 weeks' gestation.<sup>9</sup> Across all studies, only a few pregnant women with COVID-19 developed severe disease requiring oxygen support or mechanical ventilation.<sup>4,10–12</sup> Overall, the risk factors for COVID-19 among pregnant women mirror those of the general population.<sup>4,10–12</sup>

COVID-19 in pregnancy increases the risks of preterm delivery by three-fold.<sup>9</sup> Most of the preterm deliveries are iatrogenic, mostly due to maternal indications.<sup>4</sup> The disease is associated with an increased rate of Caesarean deliveries.<sup>5,9,10</sup> The evidence that COVID-19 in pregnancy may be associated with increased rates of miscarriage is insufficient.<sup>9</sup> A prospective study at a tertiary treatment centre in Turkey reported that twelve out of 533 pregnant women with COVID-19 had miscarriages. A few neonates have contracted COVID-19 during the postpartum period. However, there's no evidence of vertical transmission.<sup>4,5,9</sup> Currently, clinicians have not observed an increase in stillbirths or neonatal deaths among pregnant women with COVID-19.<sup>9</sup> Also, no evidence exists that the disease causes foetal growth restriction.<sup>9</sup>

Whether iatrogenic or not, the observation that COVID-19 is associated with preterm delivery implies that such women are subjected to antenatal corticosteroids to accelerate foetal lung maturation.<sup>13</sup> Both the American College of Obstetricians and Gynaecologists (ACOG) and the RCOG recommend that all pregnant women at risk of

imminent preterm birth receive antenatal corticosteroids to decrease the risk of neonatal respiratory complications.<sup>13</sup> This article aims to provide evidence on corticosteroid use in pregnant women with COVID-19. We literature searched from key databases that included; Google Scholar, Web of Science and PubMed using search terms like “COVID-19 in pregnancy”, “antenatal corticosteroids”, “acute respiratory distress syndrome” and “corticosteroids”. In addition, we also used the World Health Organisation (WHO) open-source databases. We then extracted and used the articles that were relevant to the topic.

## Why Corticosteroids?

Death among patients with COVID-19 is mainly due to a bout of acute respiratory distress syndrome (ARDS).<sup>14</sup> Following a direct or indirect injury to the lungs, three clinical features define ARDS.<sup>14,15</sup> They are, increased breathing rate (tachypnoea), an abnormally low blood oxygen concentration (respiratory hypoxaemia), and diffuse lung infiltrates (opacities on chest radiographs).<sup>14,15</sup> During the severe form of COVID-19, the respiratory system mounts an abnormally viscous immune response through a series of proinflammatory mediators and cytokines – a series of events clinicians have described as a cytokine storm.<sup>16</sup> It culminates in a pathological state known as secondary haemophagocytic lymphohistiocytosis.<sup>16</sup>

Normally in clinical practice, women at risk of imminent preterm delivery receive a short course of dexamethasone or betamethasone to accelerate foetal lung maturation.<sup>17,18</sup> Likewise, in severe COVID-19 condition, such patients must receive a corticosteroid that poses the least effects on the growing foetus. Corticosteroids refine the inflammatory response by decreasing the concentration of circulating proinflammatory mediators like tumour necrosis factor-alpha, interleukin-1 and interleukin-6.<sup>19</sup> They control inflammation by causing immunosuppression; as such, they have a role in managing patients experiencing ARDS.<sup>19,20</sup> The ARDS outcomes improve with prolonged corticosteroid therapy. Low-dose corticosteroids, when administered early among patients with ARDS can reduce all-cause mortality among such patients.<sup>19,20</sup>

Because pregnant women with COVID-19 have an accentuated risk of hospital admission and intensive care, they are likely to develop ARDS – and when they do, clinicians must use the corticosteroid that poses the least effect to both the mother and her foetus.

## What Corticosteroids?

The RECOVERY trial deduced that low-dose dexamethasone (6 milligrams) reduced mortality by up to one-third among COVID-19 patients on mechanical ventilation and one-fifth among those receiving supplemental oxygen.<sup>21</sup> However, it showed no benefit among COVID-19 patients with mild disease.<sup>21</sup> Pregnant women in this study received either oral prednisolone or intravenous hydrocortisone.<sup>21</sup> The RCOG recommends that pregnant women with moderate-to-severe COVID-19 should receive oral prednisolone or intravenous hydrocortisone.<sup>9</sup> But Saad et al recommend that such patients should receive methylprednisolone instead – because it has proven efficacy in acute lung injury and crosses the placental barrier in minute concentrations.<sup>22</sup> However, in sub-Saharan Africa, methylprednisolone remains an expensive drug compared to prednisolone or hydrocortisone.

The RECOVERY trial demonstrates that low-dose dexamethasone is beneficial among patients with moderate-to-severe COVID-19.<sup>21</sup> Villar et al also note that when dexamethasone is administered early to patients with established ARDS, it decreases their stay on mechanical ventilation.<sup>23</sup> But pregnant women with the same severity of the disease cannot get dexamethasone for prolonged periods because of the predicted deleterious effects on the growing foetus.<sup>21</sup>

Basing on the RECOVERY trial, the World Health Organisation (WHO) strongly recommends either oral dexamethasone or intravenous hydrocortisone in general patients with severe COVID-19.<sup>24</sup> Furthermore, WHO recommends using antenatal corticosteroids to pregnant women at high risk of preterm delivery but does not explicitly specify which corticosteroid should such women with moderate-to-severe COVID-19 receive.<sup>24</sup>

In 2017, the Society of Critical Care Medicine and European Society of Intensive Care Medicine recommended that clinicians use intravenous methylprednisolone in patients with established acute respiratory distress syndrome.<sup>25</sup> Methylprednisolone potentiates the resolution of ARDS.<sup>20,25</sup> It improves a varied spectrum of clinical outcomes and decreases hospital mortality and health care utilisation.<sup>20</sup>

During pregnancy, prolonged use of corticosteroids that readily cross the placental barrier like dexamethasone can negatively impact both the mother and the foetus.<sup>26</sup> To women, such impact includes an increased risk of endometritis and chorioamnionitis in patients with premature

rupture of membranes; increased amino acid concentration; and hyperglycaemia.<sup>26</sup> Repetitive use of corticosteroids can reduce foetal body and breathing movements; may lead to intrauterine growth restriction, low-birth weight, foetal hypoglycaemia, and an increased incidence of early-onset neonatal sepsis.<sup>26</sup> For this matter, it is not proper that pregnant women with moderate-to-severe ARDS receive dexamethasone for a prolonged period.

Murphy et al highlight that the placenta, through a distinct enzyme, metabolises several corticosteroids. These include beclomethasone; prednisolone; dexamethasone; betamethasone.<sup>27</sup> However, it does not metabolise budesonide and fluticasone. The placenta, however, metabolises more prednisolone and betamethasone than beclomethasone and dexamethasone.<sup>27</sup> It implies that the placenta helps protect the foetus from the corticosteroid side effects through this extensive metabolism to inactive products.<sup>27</sup> With this observation, prednisolone becomes a viable option.

Vichyanond et al reported that methylprednisolone achieves higher concentrations in the lungs than prednisolone.<sup>28</sup> It is so because methylprednisolone vastly distributes by volume, stays in the lung tissues longer, and is highly soluble in lipids.<sup>28</sup> Methylprednisolone penetrates the lung tissues at a higher degree when compared to prednisolone.<sup>28</sup> The body has transporter molecules like albumin that carry drugs from one point to another. Methylprednisolone exhibits a low affinity when binding to albumin – yet it does so with a very high capacity.<sup>28</sup> Contrastingly, a protein molecule (transcortin) carries prednisolone around the body.<sup>28,29</sup> Prednisolone has a very high affinity, but it binds to it with a lower capacity.<sup>29</sup> It implies that methylprednisolone more avidly reaches the lungs than prednisolone. The placenta metabolises methylprednisolone, as well as prednisolone.<sup>27</sup> It denotes that both corticosteroids are likely to get to the foetus at equivalent concentrations.<sup>27</sup> The drug that extensively distributes in the lung tissues with a limited placental transfer becomes an ideal agent to treat pregnant women with moderate-to-severe COVID-19. When such women are at risk of imminent preterm delivery, they should receive a short course of dexamethasone or betamethasone, followed by methylprednisolone for that matter.<sup>22</sup>

## Gaps in the Current Evidence and Recommendations

To date, few studies exist that are exploring corticosteroid use specifically in pregnant women with COVID-19. It

means that clinicians will still extrapolate data to formulate practice guidelines for this vulnerable population. There is limited evidence concerning the severity of COVID-19 based on the gestational age or trimesters. There is a need for further risk stratification of women in future studies.

Moreover, as of February 2021, no data presented in this article explicitly comes from the African continent which has the highest burden of maternal mortality and morbidity.<sup>30</sup> Therefore, we recommend more emphasis about the pattern of COVID-19 in pregnancy among the African population. We also recommend that more trials be conducted to assess the benefits of corticosteroids use among pregnant women with severe COVID-19. The RECOVERY trial alone is not enough to deduce practice guidelines across the entire globe. We further recommend that governments in low- and middle-income countries, for example, Uganda, ensure that corticosteroids, especially those that have proven beneficial to this vulnerable population are readily available and affordable.

## Conclusions

The above evidence favours the use of methylprednisolone than prednisolone among pregnant women with severe COVID-19. When preterm delivery is imminent, such a patient can receive the short course of dexamethasone to accelerate foetal lung maturation. She then continues getting methylprednisolone for the duration as stipulated by the country-specific COVID-19 guidelines. We explicitly note that the RCOG recommends prednisolone or hydrocortisone among pregnant women with severe COVID-19. These two drugs are not only cheaper in most low resource limited settings, but also readily available.

## Acknowledgments

We thank the institutions such as RCOG for the open-source data which was partly used for this study.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

All authors declare that they have no conflicts of interest.

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