In brief

Treatment for COVID-19 in pregnant people

29 September 2021

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• Data on COVID-19 treatments for pregnant people is continuing to emerge.
• Internationally, some colleges, for example in the UK, recommend pregnant people should be treated the same as non-pregnant people unless there are clear reasons to do otherwise.\(^1\)
• Evidence for individual drugs includes the following.
  o Corticosteroids: The RECOVERY trial protocol for pregnancy recommends prednisolone or hydrocortisone where steroids are indicated. This is because dexamethasone crosses the placenta, so a reasonable substitution is suggested to prevent unnecessary foetal exposure. While there is some data on malformation risks following first trimester, most of the best quality evidence does not suggest increased risks.\(^2\) Australian national guidelines recommend the use of antenatal corticosteroids for people at risk of preterm birth, including the use of dexamethasone in people who are receiving oxygen.\(^3\)
  o Remdesivir: Limited data suggest remdesivir is well tolerated in the second and third trimesters of pregnancy with a low risk of serious adverse events. Case reports of people receiving supplemental oxygen had resolution of this requirement after initiation of remdesivir without any major side effects or adverse events.\(^4-6\) Australian guidance recommends the use of remdesivir for pregnant or breastfeeding people with COVID-19 outside of a trial setting should not be considered routinely.\(^3\)
  o Tocilizumab: Data from the manufacturers' safety database show crude rates of malformation and miscarriage are increased in comparison to background risks, however findings are based on small numbers with confidence intervals that overlap expected rates. In a small retrospective study and case reports, it does not appear tocilizumab has detrimental effects for the mother and newborn when received during pregnancy.\(^7, 8\) Current recommendations from the USA advise against the use of interleukin-6 inhibitor tocilizumab while those in the UK support consideration of its use.\(^1, 9, 10\)
  o REGN-COV2: While the target for the monoclonal antibodies is unique to viral proteins and therefore unlikely to affect foetal development, no pregnancy exposure data is available for REGN-COV2 to establish its safety.\(^2\)
  o Prone positioning and extracorporeal membrane oxygenation (ECMO): There are case reports of successful prone-position ventilation and successful treatment with ECMO in pregnant people with COVID-19.\(^11-13\) Australian guidelines recommend that prone positioning be considered in people receiving oxygen therapy, and referral to an ECMO centre can be considered.\(^3\)
  o Venous thromboembolism prophylaxis: Australian guidelines recommend heparin at specified dosing schedules for pregnant people who are either hospitalised and have COVID-19, who have severe or critical COVID-19 or who are self-isolating at home with mild COVID-19 with additional venous thromboembolism risk factors.\(^3\)
  o Hydroxychloroquine, ivermectin, colchicine, lopinavir/ritonavir, interferon beta-1a, imatinib, azithromycin, bamlanivimab, aspirin, anakinra, magnesium sulfate therapy and baricitinib are either not currently recommended as treatment for COVID-19, or there is insufficient evidence for recommendation as a COVID-19 treatment.
COVID-19 Critical Intelligence Unit: Treatment for COVID-19 in pregnant people

Background

- Pregnant people do not appear to be more likely to contract COVID-19, however pregnant people are considered a vulnerable group and are at increased risk of severe illness from COVID-19 compared with non-pregnant people.\(^{14, 15}\)

- There are concerns that several treatment options for COVID-19 positive patients may have an impact on the foetus.

Evidence

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<th>Treatment</th>
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| Corticosteroids | • The interim results of the RECOVERY trial have demonstrated a significant reduction in 28-day mortality for individuals with COVID-19 requiring oxygen who were given steroid therapy (dexamethasone).\(^{16}\)  
  • The RECOVERY trial protocol for pregnancy recommends prednisolone 40mg orally once daily. People unable to take oral medicine are recommended to take hydrocortisone 80mg intravenously twice daily instead of dexamethasone (hydrocortisone and prednisolone are extensively metabolised by the placenta, whilst dexamethasone crosses the placenta so this substitution is suggested to prevent unnecessary foetal exposure).\(^{17}\)  
  • While there is some data on malformation risks following first trimester, most of the best quality evidence does not suggest increased risk of malformation from first trimester exposure. Small and limited studies investigating miscarriage, intrauterine death and foetal growth risks do not provide reliable evidence of increased risks. Some studies have shown increased risks of preterm delivery, but the evidence is likely confounded.\(^{2}\)  
  • One study of over 231,000 cases (pre-COVID-19) found first-trimester dexamethasone and azithromycin exposures were associated with major congenital malformation.\(^{18}\)  
  • Australian National COVID-19 Clinical Evidence Taskforce guidelines recommend:  
    o the use of antenatal corticosteroids for people at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19  
    o the use dexamethasone 6mg daily intravenously or orally for up to ten days in pregnant or breastfeeding people with COVID-19 who are receiving oxygen (including mechanically ventilated patients)  
    o Do not routinely use dexamethasone to treat COVID-19 in pregnant or breastfeeding people who do not require oxygen.\(^{3}\) |
| Remdesivir | • Remdesivir has been shown to reduce the time taken until clinical improvement in individuals with severe COVID-19.\(^{19}\) However, the SOLIDARITY trial showed no reduction in mortality rates, the need for invasive ventilation or duration of hospital stay.\(^{20}\) |
## Treatment

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| - The very limited data available to date on pregnant people suggest that remdesivir is well tolerated in the second and third trimesters of pregnancy with a low risk of serious adverse events. There is inadequate data to date for its use in the first trimester to discuss outcomes.²¹  
- A case series of 86 people (67 were pregnant, 19 immediate postpartum) were given remdesivir on a compassionate basis for severe COVID-19 infection. Although rates of pre-term delivery were high (likely related to severe COVID-19) the study demonstrated a high rate of clinical recovery.²²  
- Case reports of people receiving supplemental oxygen had resolution of this requirement after initiation of remdesivir without any major side effects or adverse events.¹¹-¹³  
- Australian National COVID-19 Clinical Evidence Taskforce guidelines recommend:  
  - Use of remdesivir for pregnant or breastfeeding people with COVID-19 outside of a trial setting should not be considered routinely.³ |

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<th>Tocilizumab</th>
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| - Evidence relating to the foetal effects following maternal use in pregnancy are limited. The largest case series published to date is provided from a review of the manufacturer’s global safety database, describing 180 prospective exposed pregnancies with a crude malformation rate of 4.5% and a crude miscarriage rate of 21.6%. Although these crude rates are increased in comparison to the background risks (malformation 2-3%, miscarriage 10-20%), the findings are based on small numbers of exposed and affected pregnancies which produced wide confidence limits that overlap the expected rates.²  
- Tocilizumab is currently offered for COVID-19 treatment as part of the RECOVERY trial.¹⁷  
- In a small retrospective study and case reports, it does not appear tocilizumab has detrimental effects for the mother and newborn when received during pregnancy.⁷, ⁸ |

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<th>REGN-COV2</th>
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| - Results from a randomised trial of 799 non-hospitalised adults with mild to moderate COVID-19 symptoms showed viral load reduction in patients treated with REGN-COV2 versus placebo at day seven. It has also been shown to prevent COVID-19 in household contacts of infected persons.²³, ²⁴  
- Whilst the target for the monoclonal antibodies are unique to viral proteins and therefore unlikely to affect foetal development, no pregnancy exposure data is available for REGN-COV2 to establish its safety.  
- REGN-CoV2 is currently offered for COVID-19 treatment as part of the RECOVERY trial.¹⁷ |
## COVID-19 Critical Intelligence Unit: Treatment for COVID-19 in pregnant people

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| Baricitinib | • Baricitinib plus remdesivir was superior to remdesivir alone in [reducing recovery time and accelerating improvement](#) in clinical status among patients with COVID-19.\(^{19}\)  
• Baricitinib is [contraindicated in pregnancy](#), as animal studies have demonstrated embryotoxicity. In [small published case reports](#) (pre-COVID-19) adverse pregnancy outcomes do not appear to be increased in comparison with their respective expected background rates.\(^{2, 25}\) |
| Venous thromboembolism (VTE) prophylaxis | • In a cohort study, use of only prophylactic-dose or treatment-dose anticoagulation was associated with [lower in-hospital mortality](#) vs no anticoagulation; however, only prophylactic-dose anticoagulation remained associated with lower mortality at 60 days.\(^{26}\)  
• Australian National COVID-19 Clinical Evidence Taskforce guidelines recommend:  
  o For pregnant or postpartum people who are admitted to hospital (for any indication) and who have COVID-19, use [prophylactic doses of anticoagulants](#), preferably low-molecular weight heparin (LMWH), e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily, unless there is a contraindication, e.g. risk for major bleeding or imminent birth.  
  o For pregnant people with severe or critical COVID-19, or where there are additional risk factors for VTE, consider using increased prophylactic dosing of anticoagulants, preferably LMWH e.g. enoxaparin 40 mg twice daily or dalteparin 5000 IU twice daily, unless there is a contraindication, such as risk for major bleeding or if platelet count is low (<30 × 10⁹/L).  
  o For pregnant or postpartum people who are self-isolating at home with mild COVID-19 and where additional risk factors for VTE are present, consider using prophylactic doses of anticoagulants, preferably LMWH e.g., enoxaparin 40 mg once daily or dalteparin 5000 IU once daily, unless there is a contraindication, such as risk for major bleeding or imminent birth.\(^{3}\) |
| Prone positioning and extracorporeal membrane oxygenation (ECMO) | • [Case reports](#) of successful [prone-position](#) ventilation in pregnant people with COVID-19 and [successful treatment with ECMO].\(^{11-13}\)  
• Australian National COVID-19 Clinical Evidence Taskforce guidelines recommend:  
  o [prone positioning](#) be considered in people receiving any form of supplemental oxygen therapy or mechanically ventilated people, although care should be taken to support the gravid uterus and reduce aorta-caval compression  
  o referrall to an ECMO centre for veno-venous ECMO can be considered for mechanically ventilated pregnant people, although this decision needs to consider gestational age, fetal |
### Treatment Evidence

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<tr>
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<tr>
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<td>viability, fetal well-being, risks and benefits to woman and baby.^{3}</td>
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<tr>
<td>Aspirin</td>
<td>• RECOVERY trial finds aspirin does not improve survival for patients hospitalised with COVID-19.^{27}</td>
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<td></td>
<td>• There are no contraindications to using low-dose aspirin to prevent placenta-mediated pregnancy complications when indicated.^{28}</td>
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<td>• Some conflicting opinion pieces, with one recommending immediate cessation of aspirin prophylaxis prescribed for pre-eclampsia upon diagnosis of SARS-CoV-2 infection, and another saying it is still essential to prescribe low-dose aspirin in people who are identified as high risk for pre-eclampsia and foetal growth restriction.^{29, 30}</td>
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<td>Magnesium sulfate therapy</td>
<td>• Limited data is available to date on magnesium sulfate therapy in COVID-19.</td>
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<td>• Case report in pregnant woman showing magnesium sulfate therapy was administered without adverse consequence and successfully lowered blood pressure.^{31}</td>
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<td>Anakinra</td>
<td>• Pregnancy data are currently limited, and although renal agenesis and oligohydramnios have been described in exposed infants, controlled studies are lacking, therefore any meaningful assessment of the teratogenic risk cannot currently be provided.^{2}</td>
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<td>Bamlanivimab</td>
<td>• Bamlanivimab has been found to be ineffective in treating hospitalised patients with COVID-19.^{32}</td>
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<td>• No pregnancy exposure data are currently available.</td>
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<td>Ivermectin</td>
<td>• A Cochrane review found based on the current very low- to low-certainty evidence, there are uncertainties about the efficacy and safety of ivermectin used to treat or prevent COVID-19.^{33}</td>
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<td>• Safety in pregnancy has not been established and therefore should not be used.^{34}</td>
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<td>Colchicine</td>
<td>• There is currently insufficient evidence to recommend either for or against the use of colchicine for the treatment of non-hospitalised patients with COVID-19, and its use is not recommended in hospitalised patients.^{35}</td>
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<td>Hydroxychloroquine</td>
<td>• Hydroxychloroquine has not shown to be effective for the treatment of COVID-19.^{36}</td>
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<tr>
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<td>• It is not recommended for the treatment of COVID-19 in Australia.^{3}</td>
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<td>Azithromycin</td>
<td>• Azithromycin has not been shown to benefit clinical outcome including clinical status or mortality, when added to standard care (which included hydroxychloroquine) in treating patients admitted to hospital with COVID-19.^{37}</td>
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<td>• One study of over 231,000 cases (pre-COVID-19) found first-trimester dexamethasone and azithromycin exposures were associated with major congenital malformation. (^{18})</td>
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<td>Lopinavir/ritonavir</td>
<td>• Lopinavir/ritonavir has not shown to be effective for the treatment of COVID-19 and is therefore not recommended for treating COVID-19 in pregnancy. (^{20})</td>
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<td>Interferon beta-1a</td>
<td>• The SOLIDARITY trial showed no reduction in mortality, initiation of ventilation or hospitalisation duration in COVID-19 patients treated with interferon beta-1a or with interferon beta-1a and lopinavir when compared to standard care. (^{20})</td>
</tr>
<tr>
<td>Imatinib</td>
<td>• There is insufficient evidence for the off-label use of imatinib in patients with COVID-19. (^{38})</td>
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| Other treatment options   | • Clinical trials of several other treatment options are recorded in the EU register, including camostat mesilate, sarilumab and sargramostim. No pregnancy exposure data were located for these medications.  
• Australian National COVID-19 Clinical Evidence Taskforce guidelines recommend:  
  ○ other disease modifying treatments should not be used outside of randomised trials, with emphasis that trials enrolling pregnant and breastfeeding people are needed. \(^{3}\) |

**Published recommendations**

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<td>Australian guidelines for the clinical care of people with COVID-19: Pregnancy and perinatal care</td>
<td>• Recommendations reflect special populations, including pregnant people (see Table 1).</td>
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<tr>
<td>National COVID-19 Clinical Evidence Taskforce, August 2021(^{39})</td>
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</table>
| COVID-19 treatment guidelines: Special considerations in pregnancy | • Potentially effective COVID-19 treatments should not be withheld from pregnant people because of theoretical concerns about the safety of those treatments.  
• There is no pregnancy-specific data on the use of anti-SARS-CoV-2 monoclonal antibodies, but pregnant people may be considered for COVID-19 treatment, particularly where there are additional risk factors for severe disease.  
• Remdesivir should not be withheld from pregnant people if it is otherwise indicated. |
| National Institutes of Health, July 2021\(^{9}\)        |                                                                                                                                                                                                          |

*In brief documents are not an exhaustive list of publications but aim to provide an overview of what is already known about a specific topic. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.*
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| COVID-19 Critical Intelligence Unit: Treatment for COVID-19 in pregnant people | • There is insufficient evidence on the safety of using ivermectin, GM-CSF inhibitors, interleukin-1 inhibitors or the interleukin-6 inhibitors sarilumab or siltuximab in pregnant people.  
  • There are no data on using nitazoxanide or colchicine to treat COVID-19 in pregnant people.  
  • Dexamethasone is recommended in hospitalised pregnant people with COVID-19 who are mechanically ventilated or who require supplemental oxygen but are not mechanically ventilated  
  • The risk of fluvoxamine or kinase (JAK or BTK) inhibitors should be balanced with potential benefit.  
  • Intravenous immunoglobulin is used in pregnancy for other indications such as immune thrombocytopenia.  
  • Current recommendations advise against the use of interleukin-6 inhibitor tocilizumab. |
| COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics              | • Monoclonal antibody treatments have not been tested specifically in pregnant people and more data are needed to make a recommendation for use.  
  • Antenatal corticosteroids may be used up to 34 weeks’ gestation.                                                                                                                                     |
| The American College of Obstetricians and Gynecologists, July 2021   |                                                                                                                                                                                                          |
| Management considerations for pregnant patients with COVID-19        | • Remdesivir is recommended for pregnant people with COVID-19 who meet the criteria for compassionate use.                                                                                              
  • Dexamethasone is recommended for pregnant people who require oxygen or mechanical ventilation.                                                                                                
  • There is no absolute contraindication to the use of monoclonal antibodies in pregnant people where it is otherwise indicated.                                                                        |
| Society for Maternal-Fetal Medicine, February 2021                   |                                                                                                                                                                                                          |
| Coronavirus (COVID-19) infection in pregnancy                       | • Pregnant and postpartum patients with COVID-19 should be treated the same as non-pregnant people unless there is a clear reason otherwise.                                                        
  • Antibiotics may be used for any additional bacterial infection.  
  • Corticosteroids should be given for 10 days or up to discharge if oxygen supplementation or ventilatory support is required.                                                                      
  • Strongly consider tocilizumab or REGEN-COV monoclonal antibodies in certain circumstances.                                                                                                       
  • Remdesivir should only be considered if a patient is not improving or is deteriorating.                                                                                                           
  • Azithromycin, hydroxychloroquine, and lopinavir/ritonavir not effective and not recommended.                                                                                                       |
| The Royal College of Midwives and Royal College of Obstetricians and Gynaecologists, UK, August 2021 |                                                                                                                                                                                                          |
| COVID-19 infection guidance for maternity services                   | • Treatment of pregnant people with COVID-19 should be similar to the treatment of non-pregnant people.                                                                                                |
COVID-19 Critical Intelligence Unit: Treatment for COVID-19 in pregnant people

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| Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland, April 2020 | - Hydroxychloroquine does not pose a risk to the fetus at the recommended dose.  
- Azithromycin is compatible with pregnancy.  
- Lopinavir/ritonavir may be used where the benefits outweigh the risks.  
- Remdesivir should not be excluded for seriously ill pregnant people eligible for access under compassionate use.  
- Limited data is available on the use of tocilizumab.  
- Analgesics, steroids and antibiotics can also be used. |

To inform this brief, for the evidence table, Medications used to treat COVID-19 in pregnancy published in December 2020 in the UK was used as the initial base of information. PubMed searches were then conducted to update the information in the table using terms pregna*[ti] AND covid-19 AND (“individual drug name from table”) on 30 August 2021. Grey literature was searched on Google and Google Scholar using terms related to COVID-19 AND pregnancy AND treatment AND guidelines on 30 August 2021.

References


27. Recovery. Statement from the RECOVERY trial chief investigators, 8 June 2021: RECOVERY trial finds aspirin does not improve survival for patients hospitalised with COVID-19 [Internet].


32. Mahase E. Covid-19: FDA authorises neutralising antibody bamlanivimab for non-admitted patients. BMJ. 2020;371:m4362. DOI: 10.1136/bmj.m4362


38. Zhao H, Mendenhall M, Deininger MW. Imatinib is not a potent anti-SARS-CoV-2 drug. Leukemia. 2020 1 November;34(11):3085-7. DOI: 10.1038/s41375-020-01045-9

