A review of remdesivir for COVID-19 in pregnancy and lactation

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Mounting evidence suggests that pregnant people have an elevated risk of severe COVID-19-related complications compared with their non-pregnant counterparts, underscoring the need for effective prevention and treatment strategies. However, despite progress in innovative and flexible trial designs during the COVID-19 pandemic, regressive policies excluding pregnant and breastfeeding people from biomedical research persist. Remdesivir, a broad-spectrum antiviral, was the first drug licensed for the treatment of COVID-19, based on data showing it reduced the time to recovery in hospitalized patients. Pregnant and breastfeeding people were specifically excluded from all clinical trials of remdesivir in COVID-19, but data are accumulating from post-marketing registries, compassionate use programmes and case series/reports. In this review we synthesize these data and highlight key knowledge gaps to help inform clinical decision-making about its use in pregnancy and lactation.

Background

Over the last 18 months, much has been learned about the effects of COVID-19 on pregnancy and perinatal outcomes. The results are sobering; higher rates of severe disease and complications have been documented amongst pregnant people in both high-income countries and low- and middle-income countries.1–5 In addition, severe and critical COVID-19 in pregnancy has been associated with elevated rates of premature birth and neonatal morbidities.1–7

The management of pregnant people with COVID-19 presents unique clinical and ethical challenges, which are amplified by the relative scarcity of rigorous, high-quality data about safety and efficacy of interventions in this population.8,9 Despite a clear medical need, pregnant people continue to be routinely excluded from biomedical research, hampering efforts to provide evidence-based care.9

Remdesivir is a nucleoside prodrug with broad-spectrum activity against human and zoonotic coronaviruses.10 It was the first drug licensed for the treatment of COVID-19 and has been shown to shorten the time to recovery in hospitalized patients requiring oxygen therapy.11 Its impact on mortality, however, is uncertain11–15 and this uncertainty is reflected in the heterogeneity of consensus treatment guidelines, with some recommending for, and others against, its use in hospitalized patients with severe COVID-19.16–20

Pregnant and breastfeeding people were specifically excluded from all clinical trials evaluating remdesivir for COVID-19,11–15 and as such, there is no direct evidence of efficacy in this population. Pregnant people were eligible for an earlier Phase III trial evaluating remdesivir for Ebola virus infection; six pregnant patients were enrolled in the remdesivir arm (3.4% of the participants who were randomized to remdesivir) and there were no significant maternal, fetal or newborn adverse events reported in this subgroup.21 Remdesivir has been used outside of clinical trials in pregnant people with COVID-19 and data on safety are accumulating from post-marketing registries, compassionate use programmes and case series/reports.22–33 The aim of this review was to summarize and synthesize these data to help inform clinical decision-making about remdesivir’s use in pregnancy and lactation. To set the evidence in context, we briefly review background information on adverse pregnancy and fetal outcomes in general, and the effect that COVID-19 has on pregnancy and perinatal outcomes.

Sources

Literature searches of PubMed and Medline were conducted using various combinations of the search terms remdesivir, GS-5734, GS-441524, pregnancy, lactation, breastfeeding, pharmacokinetics, COVID-19 and SARS-CoV-2. Reference lists of relevant articles were examined to identify sources not captured in the electronic literature search. Additional data were obtained from the US FDA regulatory approval review documents.

Adverse pregnancy and fetal outcomes

Adverse pregnancy outcomes include elective terminations, fetal losses, preterm birth (<37 weeks) and maternal mortality.34,35 Fetal loss can result from spontaneous abortion, during the first...
20 weeks of gestation, or from stillbirth, after 20 weeks.36 Most spontaneous abortions occur in the first trimester as the result of chromosomal abnormalities.36 Global stillbirth rates show large disparities between developed and developing countries, with an estimated overall rate of 1.8% (2015) but a range from 0.3% in developed regions to 2.9% in sub-Saharan Africa.37 Preterm births may be spontaneous or iatrogenic (i.e. medically indicated). The estimated global preterm birth rate in 2014 was 10.6%, with significant differences by region, from 8.7% in Europe to 13.4% in North Africa.38 Maternal mortality refers to deaths due to complications of pregnancy or childbirth as well as deaths occurring within 42 days of pregnancy termination.35 It is standardized as the maternal mortality ratio, defined as the number of maternal deaths per 100,000 live births during a given time period. Globally, the annual maternal mortality ratio was 211 in 2017 but varied widely from 5 in Western Europe to 533 in sub-Saharan Africa.39

Important adverse fetal outcomes include low birth weight (<2.5 kg) and birth defects.35 Low birth weight affects approximately 15% of live births globally and tracks with prematurity.19 The overall background prevalence of birth defects is between 3% and 4%, depending on the definition used, population studied and time period of follow-up.16,40 Birth defects secondary to drug exposure account for less than 1% of all birth defects.34 The embryonic period, between Weeks 3 and 8, marks the period of greatest sensitivity to the effects of teratogens.34

**Effect of COVID-19 on pregnancy outcomes**

Early in the COVID-19 pandemic it was unclear whether pregnancy was a risk factor for more severe illness. Initial data, mainly in the form of case series and centre experiences, were difficult to interpret, lacked appropriate comparator groups and were limited by other potential biases. Now that larger datasets are available, it is clear that pregnant people are at heightened risk of severe COVID-19-related complications compared with their non-pregnant counterparts, particularly when infection occurs in the third trimester.1–5 For example, the risk of ICU admission and mechanical ventilation are approximately 2–4 times higher than those of non-pregnant populations of the same age.1,2,4 In addition, although the absolute risk of death in pregnant people with COVID-19 is low, it is many times higher than that of non-infected people of similar gestation.1,2 The majority of deaths have been concentrated in less-developed regions where comprehensive intensive care resources may be limited.2

The emergence of new variants has been linked to trends of increasing illness severity in pregnant and peripartum people, but a fulsome understanding of this association is still evolving.53 Similar to the general population, pre-existing comorbidities such as chronic hypertension, diabetes and obesity are additional risk factors for severe disease in pregnant people.12,57 The magnitude of risk to pregnant people is also amplified in minority populations.1,2,5,7

Multiple studies have shown that severe or critical COVID-19 infection during pregnancy increases the risk of preterm delivery and neonatal respiratory morbidity.1–7 The majority of preterm deliveries in severe and critical COVID-19 cases appear to be iatrogenic rather than due to direct effects of infection or maternal illness.12,26 In keeping with elevated rates of prematurity, neonatal ICU admissions and respiratory disorders have also been increased.1–5,7 Maternal SARS-CoV-2 infection has not been linked to birth defects, although data on infection in early pregnancy are limited. Some, but not all, studies have suggested that stillbirths are more common among pregnant people with COVID-19, although the numbers overall are low and estimates are imprecise.1–5,43

Data regarding intrauterine SARS-CoV-2 transmission have been reassuring. Although it has been reported,44 intrauterine transmission appears to be rare.2,4,45 Similarly, transmission via breastmilk seems to be unlikely.46 Finally, when appropriate precautions are taken, the risk of mother-to-infant postnatal transmission appears to be low.47

**Preclinical data**

Remdesivir has been evaluated in vivo and in vitro assays and was not found to exert genotoxic effects. For animal studies, remdesivir has been assessed in rat fertility and prenatal and postnatal studies, as well as rat and rabbit embryo-fetal developmental studies.48 In a prenatal study in rats, female rats exposed to remdesivir 10 mg/kg/day (1-fold exposure of regular human doses) exhibited a lower mean number of corpora lutea, and consequently lower mean numbers of implantation sites and viable embryos accompanied by lower mean ovary and uterus/cervix/oviduct weights. These findings were considered to be related to remdesivir exposure and the ‘no observed adverse effect level’ (NOAEL) for female reproductive and embryonic toxicity was deemed to be 3 mg/kg/day, which provides approximately 0.34-fold exposure to regular human doses. No adverse effects on intrauterine growth, survival and fetal morphology were observed in embryo-fetal development studies in pregnant rats and rabbits with exposures up to four times higher than those achieved in humans with recommended dosing.48

Remdesivir transplacental transfer studies have not been completed; however, reasonable predictions can be made based on its chemistry and pharmacokinetics. Remdesivir is a monophosphoramide prodrug; following IV administration it is rapidly hydrolysed by intracellular esterases to a nucleoside monophosphate analogue and requires several additional steps of metabolism to generate the active intracellular nucleotide triphosphate analogue.10 This suggests that remdesivir itself is unlikely to cross the placenta in clinically important amounts, but characteristics of major circulating metabolites, such as long half-lives, low molecular weights and high unbound fractions,10 suggest that they may have greater placental transfer.

**Clinical data**

Most of the published clinical experience with remdesivir in pregnant women comes from (1) Gilead’s global safety database, which includes both Ebola virus and COVID-19 patients; and (2) the COVID-19 compassionate use programme (Table 1).23,32 It is possible that these sources included overlapping cases. The global safety database included 156 cases of remdesivir exposure during pregnancy (cumulative to August 2020).32 Pregnancy outcomes were documented for less than one-third and included 33 live births and 13 adverse pregnancy outcomes (7 spontaneous abortions, 2 induced abortions and 4 stillbirths). Of the 13 cases with adverse pregnancy outcomes, 9 were reported in pregnant patients treated with remdesivir for Ebola virus
| First author, publication year | Design | Setting | Number of patients | Gestational age at time of RDV initiation | Concomitant COVID-19-specific medications/biologics | Maternal COVID-19 severity | Birth outcomes | Maternal outcomes |
|-------------------------------|--------|---------|--------------------|------------------------------------------|-----------------------------------------------|-----------------------------|----------------|------------------|
| Burwick 1RM, 2020<sup>23</sup> | Observational study | Gilead Sciences compassion-ate use programme | N = 86 | 67/86 pregnant 28 (range 14–39) GW 19/86 postpartum | Pregnant: 25/67 hydroxychloroquine 23/67 azithromycin 1/67 tocilizumab Postpartum: 7/19 hydroxychloroquine 2/19 azithromycin 1/19 tocilizumab | Pregnant: 27/67 IMV 44/67 ICU 46/67 high-risk pregnancy Postpartum: 17/19 IMV 19/19 ICU | 26 deliveries in pregnant cohort 19/26 CD (17 emergent CD) 18/26 very preterm 1 spontaneous abortion at 17 GW–complicated by S. aureus IE Neonatal SARS-CoV-2 infection status NR | Pregnant: 62/67 recovered by HD 28 Postpartum: 17/19 recovered by HD 28 1/19 death Grade 3 ALT elevation 7/86 Grade 3 AST elevation 4/86 AE leading to RDV d/c 7/86 NR |
| FDA CDER, 2020<sup>32</sup> | Gilead Sciences global safety database | Global | N = 156 | GW NR | NR | NR for overall cohort, see text for details | 33/46 live births 13/46 adverse pregnancy outcome – 2 induced abortions, 7 spontaneous abortions, 4 stillbirths 5 congenital abnormalities | 17/24 clinical recovery by HD 7 17/17 who started RDV ≤48 h of admission recovered 0/7 who started RDV >48 h of admission recovered No maternal deaths 8/24 elevated transaminase elevations |
| Nasrallah S, 2021<sup>33</sup> | Case series | USA | N = 24 | (subgroup of 748 patient cohort) 6–40 GW | 13/24 corticosteroids | 15/24 moderate 2/24 critical | 8/24 CD; 11/24 GD; 5/24 ongoing at publication 4/19 preterm 1/19 fetal growth restriction 18/19 neonates SARS-CoV-2 negative | 17/24 clinical recovery by HD 7 17/17 who started RDV ≤48 h of admission recovered 0/7 who started RDV >48 h of admission recovered No maternal deaths 8/24 elevated transaminase elevations |
| Pierce-Williams RAM, 2020<sup>31</sup> | Cohort study | USA | N = 16 | (subgroup of 65 patient cohort) | NR separately for RDV subgroup | 3/16 severe 13/16 critical | | |
| McCoy JA, 2020<sup>38</sup> | Case series | USA | N = 5 | 16–31 GW | 5/5 hydroxychloroquine | 3/5 IMV 3/5 ICU | 3/5 CD; 1/5 GD; 1/5 ongoing at publication 4/4 neonates SARS-CoV-2 negative | 5/5 recovered by HD 5–19 3/5 increases in AST, ALT 1/5 RDV d/c due to increases in ALT, AST |

Continued
| First author, publication year | Design       | Setting  | Number of patients | Concomitant COVID-19-specific medications/ biologics | Maternal COVID-19 severity | Birth outcomes                                      | Maternal outcomes                                      |
|--------------------------------|--------------|----------|--------------------|----------------------------------------------------|---------------------------|----------------------------------------------------|--------------------------------------------------------|
| Igbinosa I, 2020              | Case series  | USA      | N = 3              | 0/3 corticosteroids NR for other medications       | 1/3 NIV                  | 1/3 VD at 37 w + 2 d (for IHCP) Birth weight NR Neonatal SARS-CoV-2 infection status NR 2/3 ongoing at publication | 3/3 recovered and discharged by HD 6–9 1/3 developed increased AST, ALT after three RDV doses, ultimately diagnosed with IHCP |
| Maldarelli GA, 2020           | Case report  | USA      | N = 1              | Hydroxychloroquine (held when RDV initiated) Tocilizumab | Supplemental O2 ICU       | Uncomplicated VD at term Birth weight NR Ongoing at publication | Recovered and discharged HD 9                             |
| Naqvi M, 2020                 | Case report  | USA      | N = 1              | Convalescent plasma Hydroxychloroquine Azithromycin | Supplemental O2 ICU       | Recovered and discharged on HD 8 Recovered and discharged on HD 14                                      |
| Anderson J, 2020              | Case report  | USA      | N = 1              | Hydroxychloroquine (for RA) Dexamethasone Convalescent plasma Azithromycin | MV ICU                   | Ongoing at publication CD at 29 GW + 1 d Birth weight 1310 g Apgar scores 3 and 6 Infant negative SARS-CoV-2 PCR at 3 and 14 d | Recovered and discharged on HD 6 Transferred to an intermediate care facility on HD 40 and discharged home on HD 52 with supplemental O2 and nursing care Transferred to acute rehabilitation facility on HD 19 |
| Dande R, 2021                 | Case report  | USA      | N = 1              | Methyprednisolone Convalescent plasma               | MV ICU                   | CD at 36 GW + 2 d Apgar scores 11 25 410 Infant negative SARS-CoV-2 PCR | Transferred to acute rehabilitation facility on HD 19 |
| Jacobson J, 2021              | Case report  | USA      | N = 1              | Convalescent plasma Hydroxychloroquine Azithromycin | MV ICU                   |                                                    |                                                        |
| Pelayo J, 2020                | Case report  | USA      | N = 1              | Methyprednisolone Convalescent plasma               | MV ICU                   |                                                    |                                                        |

AE, adverse event; CD, Caesarean delivery; d, day(s); d/c, discontinuation; GW, gestational weeks; HD, hospital day; IE, infective endocarditis; IHCP, intrahepatic cholestasis of pregnancy; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; NR, not reported; RA, rheumatoid arthritis; RDV, remdesivir; VD, vaginal delivery.
infection and 4 received remdesivir for COVID-19. All patients with COVID-19 who experienced adverse pregnancy outcomes were critically ill and required invasive mechanical ventilation within 24 h of remdesivir initiation. Five cases of congenital abnormalities were also identified; in all cases, remdesivir exposure occurred after the first trimester.

Sixty-seven pregnant people received remdesivir through the COVID-19 compassionate use programme during a 1 month period early in the pandemic (March–April 2020). Most (>90%) were enrolled in the USA. The median gestational age was 28 weeks (range 14–39 weeks) with no first trimester exposures. A high proportion of critically ill pregnant patients were included: 67% were admitted to the ICU and 40% received invasive mechanical ventilation. Overall, 93% recovered within 28 days. In keeping with results in non-pregnant patients, pregnant patients not requiring invasive mechanical ventilation had the highest rates of recovery (98%) and the shortest median time to recovery (5 days). Amongst 26 deliveries, 69% were delivered very preterm (24–32 weeks gestation). No neonatal deaths occurred during the observation period and there were no congenital abnormalities observed at birth (M. Das, Gilead Sciences; personal communication, 3 May 2021). There was one spontaneous abortion at 17 weeks' gestation in a woman with concurrent Staphylococcus aureus bacteremia, endocarditis and septic arthritis and one maternal death after delivery, which was attributed to COVID-19.

The recovery rate in this report is reassuring, particularly considering the high prevalence of critical illness at baseline. Case series and single case reports also support rapid recovery in pregnant people treated with remdesivir for COVID-19, with most being discharged from hospital within 6–9 days (Table 1). However, without a control group the contribution of remdesivir to recovery is unclear.

The high rate of very preterm delivery reported in the compassionate use programme is troubling, but without an appropriate comparator group and contextual details it is difficult to determine whether there is a causal link with remdesivir. As noted previously, COVID-19 infection itself in pregnancy carries an elevated risk of critical illness and prematurity.23,25,27-29,33

Conclusions

Pregnant people have been recognized as a medically complex population during infectious disease pandemics since the pre-antibiotic era and continue to be disproportionately impacted during the current pandemic. Prevention and treatment strategies are therefore critically important to improve maternal and neonatal outcomes. However, there has been little progress in the equitable inclusion of pregnant and breastfeeding people in biomedical research, forcing clinicians and their pregnant patients to weigh potential benefits and harms of interventions based on very little information.8,9

To assist in this decision-making, we reviewed data on remdesivir in pregnancy and lactation from a variety of sources. Although our review does not reveal serious safety signals, it is clear that the available data have serious limitations and are insufficient to support clear, evidence-based recommendations.
delineate the complete spectrum of potential adverse outcomes associated with exposure to remdesivir during pregnancy and lactation. Importantly, there are very few data on remdesivir exposure in the first trimester, when organogenesis occurs. In addition, requisite pharmacokinetic data in pregnancy are currently lacking. The role of remdesivir in preventing vertical or postnatal SARS-CoV-2 transmission is also unclear. Diligent follow-up and documentation of outcomes in pregnant people with COVID-19 treated with remdesivir will be important moving forward. Greater regulatory push is clearly needed to ensure studies to obtain pregnancy data are expedited.

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