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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 uncertain[11–15] 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.[34] 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.[35]

Important adverse fetal outcomes include low birth weight (<2.5 kg) and birth defects.[34] Low birth weight affects approximately 15% of live births globally and tracks with prematurity.[39] 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.[34,40] 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.[41] 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.[1,2,5,7] The magnitude of risk to pregnant people is also amplified in minority populations.[1,2,5]

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.[42] 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 in vitro and in vivo 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 monophosphoramidate 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

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Table 1. Summary of studies of remdesivir in pregnancy for COVID-19

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[23]	Observational study / Gilead Sciences compassionate use programme	91% USA / 9% Europe	N = 86 / 67/86 pregnant / 28 (range 14–39) GW / 19/86 postpartum	Pregnant: 25/67 hydroxychloroquine / 23/67 azithromycin / 1/67 tocilizumab / 1/67 lopinavir/ritonavir / 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
FDA CDER, 2020[32]	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	NR
Nasrallah S, 2021[33]	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 VD; 5/24 ongoing at publication / 4/19 preterm / 1/19 fetal growth restriction / 19/19 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[31]	Cohort study	USA	N = 16 (subgroup of 65 patient cohort)	NR separately for RDV subgroup	3/16 severe / 13/16 critical	NR separately for RDV subgroup	NR separately for RDV subgroup
McCoy JA, 2020[28]	Case series	USA	N = 5 / 16–31 GW	5/5 hydroxychloroquine	3/5 IMV / 3/5 ICU	3/5 CD; 1/5 VD; 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

Table 1. *Continued*

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
Igbinosa I, 2020[25]	Case series	USA	N = 3 25–34 GW	0/3 corticosteroids NR for other medications	1/3 NIV 1/3 ICU	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[27]	Case report	USA	N = 1 35 GW + 1 d	Hydroxychloroquine (held when RDV initiated)	Supplemental O_2 ICU	Uncomplicated VD at term Birth weight NR	Recovered and discharged HD 9
Naqvi M, 2020[29]	Case report	USA	N = 1 22 GW + 6 d	Tocilizumab	Supplemental O_2	Ongoing at publication	Recovered and discharged on HD 8
Anderson J, 2020[22]	Case report	USA	N = 1 23 GW	Convalescent plasma Hydroxychloroquine Azithromycin	MV ICU	Ongoing at publication	Recovered and discharged on HD 14
Dande R, 2021[24]	Case report	USA	N = 1 29 GW	Hydroxychloroquine (for RA)	Supplemental O_2	Ongoing at publication	Recovered and discharged on HD 6
Jacobson J, 2021[26]	Case report	USA	N = 1 26 GW	Dexamethasone Convalescent plasma Azithromycin	MV ICU	CD at 29 GW + 1 d Birth weight 1310 g, Apgar scores 3^1 and 6^5 Infant negative SARS-CoV-2 PCR at 3 and 14 d	Transferred to an intermediate care facility on HD 40 and discharged home on HD 52 with supplemental O_2 and nursing care
Pelayo J, 2020[30]	Case report	USA	N = 1 36 GW + 2 d	Methylprednisolone Convalescent plasma	MV ICU	CD at 36 GW + 2 d Apgar scores 1^1 2^5 4^{10-20} Infant negative SARS-CoV-2 PCR	Transferred to acute rehabilitation facility on HD 19

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).[23] 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* bacteraemia, 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.[23] 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).[22–25,27–29,33] 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[23] 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 preterm delivery, especially in the setting of critical illness.[1–5] In addition, the rate of very preterm delivery in patients followed through this programme who received remdesivir postpartum was numerically similar (63%) to those who received it during pregnancy.[23] If nothing else, it is disappointing that this occurred despite the use of remdesivir, underscoring the need for more effective therapies in pregnant patients.

It is clear that published reports of remdesivir treatment in pregnant people lack many salient details (Table 1).[22–33] For example, in the publications from the safety database and compassionate use programme, birth weight, the need for neonatal ICU admission and SARS-CoV-2 perinatal infections were not reported.[23,32] Many of these outcomes were also missing in the other case series and reports outlined in Table 1. The small number of documented negative PCR results in infants of mothers treated with remdesivir (Table 1) are insufficient to determine whether remdesivir can prevent rare cases of perinatal transmission.

Increases in transaminases have been described in both pregnant and non-pregnant individuals treated with remdesivir.[10,23,25,28,33] The mechanism and clinical importance remain unclear. Nearly 40% of people enrolled in the compassionate use programme experienced treatment-emergent graded liver

enzyme abnormalities but grade 3 abnormalities were uncommon (ALT, 5%; AST, 9%).[23] These liver enzyme abnormalities might be related to remdesivir, COVID-19, other pregnancy-related causes (e.g. preeclampsia) or unrelated causes. In one report, a pregnant patient treated with remdesivir was ultimately diagnosed with intrahepatic cholestasis of pregnancy,[25] highlighting the need to keep the differential open when pregnant patients show signs of liver injury.

Pharmacokinetics

Pregnancy is associated with multiple physiological, anatomical and biochemical changes that can dramatically impact the pharmacokinetics of antivirals, potentially leading to subtherapeutic exposure, unpredictable adverse effects or accelerated resistance.[49] Remdesivir pharmacokinetic data were derived from healthy non-pregnant adult volunteers. Sparse pharmacokinetic results from three critically ill patients with COVID-19 have also been reported,[50,51] but no data describing remdesivir pharmacokinetics in pregnancy are available. Simulation studies suggest pregnancy-related increases in glomerular filtration rate and renal tubular secretion may increase elimination of remdesivir's major active extracellular metabolite.[52] Additionally, pregnancy-related changes in plasma protein concentrations due to displacement from protein binding sites and volume expansion may alter unbound concentrations of remdesivir and its metabolites,[52] potentially leading to more rapid clearance. Higher doses or more frequent administration may be required during pregnancy to match exposure seen in non-pregnant populations. However, the clinical importance of altered exposure is unclear since pharmacokinetic/pharmacodynamic efficacy and toxicity targets have not been established.

Breastfeeding

There are no data on the use of remdesivir in nursing mothers. Since remdesivir undergoes extensive first-pass metabolism, infants are unlikely to absorb clinically important amounts of remdesivir from breastmilk.[53] However, systemic exposure to metabolites could result from breastfeeding. Reassuringly, no adverse effects were documented in the small number of infants who received remdesivir for treatment of Ebola virus infection or COVID-19.[54,55]

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.[1–5] 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

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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Transparency declarations

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