

## Remdesivir for the treatment of COVID-19 in pregnancy

The devastating coronavirus disease 2019 (COVID-19) global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by the World Health Organisation (WHO) in March 2020 and now at over 9 months since its declaration, it continues to claim vast numbers of lives all over the world.<sup>1</sup> There is no evidence that pregnant women are more susceptible to SARS-CoV-2 infection than the general population; however, pregnancy-associated immunological changes could potentially render pregnant individuals more vulnerable to severe COVID-19 as has been previously observed with influenza A/H1N1, severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS).<sup>2</sup> Evidence from the United States (US) cohort study suggests that severe COVID-19 in pregnancy (predominantly in the third trimester) is associated with iatrogenic-associated preterm birth (75% delivered preterm).<sup>3</sup> Data from the UK cohort study of 427 pregnant women hospitalised with COVID-19 estimated an incidence of admission to hospital with confirmed SARS-CoV-2 infection of 4.9 per 1000 maternities.<sup>2</sup> In this study, 81% were in the third trimester or peripartum also suggesting that severe illness may be more common later in pregnancy. Ten percent (41/427) needed Level 3 critical care, of whom 80% (33/41) delivered their child while admitted with COVID-19 (66% delivered due to worsening respiratory condition). Overall mortality in pregnant women admitted with confirmed SARS-CoV-2 infection was 1.2% (5/427; three of whom died directly from complications of COVID-19). COVID-19 is responsible for a significant disease burden among pregnant women and although this may not be in excess of that observed in the general population, potential treatment options are limited even further in pregnant women, in part through their exclusion (often for justifiable reasons) from clinical trials. A review of COVID-19 treatment studies (of nonbiological drugs) at two specific time points (April 7–20, 2020 and July 10–15, 2020) found that pregnant women were excluded from 80% and 75% of studies during the first and second time points, respectively.<sup>4</sup>

Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent RNA polymerase was identified as a potential candidate for the treatment of COVID-19 after it was demonstrated to inhibit SARS-CoV-2 replication *in vitro*.<sup>5,6</sup> In a large multicentre, international double-blind, randomised, placebo-controlled trial of 1062 patients with COVID-19 with evidence of lower respiratory tract infection, intravenous remdesivir (for 10 days or until hospital discharge or death) was associated with a shortened time to recovery when compared with placebo (median recovery time of 10 days with remdesivir vs. 15 days with placebo,  $p < 0.001$ ) and remdesivir was also associated with a shortened time to discharge from hospital.<sup>6</sup>

All-cause mortality was 11.4% with remdesivir and 15.2% with placebo. Adverse events occurred in 24.6% of the remdesivir group and 31.6% of the placebo group. This study excluded pregnant and breast-feeding women. A recent systematic review of remdesivir in hospitalised COVID-19 patients found that remdesivir significantly increased the recovery rate (by 22% and 14% on Days 7 and 28, respectively) compared to the control group, and significantly reduced 14-day mortality (by 36%) among moderate and severe COVID-19 patients but there was no significant difference in 28-day mortality.<sup>7</sup>

Remdesivir has been the first drug to be approved by the Food and Drug Administration (FDA) in the United States (Emergency Use Authorisation was first granted on May 1, 2020) for use in children and adults hospitalised with COVID-19 and has also been approved in several other parts of the world. Pregnant women, however, are excluded from many recommendations for the use of remdesivir in COVID-19 largely due to a lack of clinical trial data. Its administration in pregnancy has primarily been on a compassionate use basis. Safety data from the manufacturer report that at clinically relevant doses of remdesivir, no reproductive developmental toxicity was observed in animals (Remdesivir Investigator's Brochure, Gilead Sciences). Human data for the use of this agent in pregnant women with COVID-19 are extremely limited. In an earlier study of remdesivir in the treatment of Ebola virus disease, six pregnant women were assigned to receive remdesivir and there were no significant foetal/newborn, pregnancy, or maternal adverse events reported in any of the members of this subgroup.<sup>8</sup> Additionally, remdesivir has been used in the treatment of congenital Ebola virus infection in a neonate born to an Ebola virus-positive woman; the neonate tolerated the 12-day course of remdesivir well with no evidence of drug toxicity and at 12-month follow-up the child remained well.<sup>9</sup>

The largest data for remdesivir in pregnant women with COVID-19 come from a US study by Burwick et al. in which 67 hospitalised pregnant patients (82% were  $\geq 24$  weeks gestation) with COVID-19 were treated on a compassionate use basis with remdesivir (and no other specific investigational therapies for COVID-19 were administered to these patients).<sup>10</sup> Ninety-three percent recovered from their illness despite 67% requiring intensive care unit (ICU) admission. Remdesivir was generally well tolerated; incidence of serious adverse events was 18% (33% experienced an adverse event) and the majority of adverse events were deemed to be related to pregnancy and/or underlying disease. The study did not include a control group, the inclusion of which may have aided in addressing any uncertainties regarding whether similar adverse events rates would be observed in this patient population even in the absence of remdesivir administration.

**TABLE 1** Published studies of remdesivir in the treatment of coronavirus disease 19 (COVID-19) in pregnancy

Study location	Number of pregnant patients who received remdesivir	Age	Gestation of pregnancy	Duration of symptoms before remdesivir	Comorbidities	Dose/duration of remdesivir	Other SARS-CoV-2/COVID-19 targeted therapies administered	Level of care required	Outcome	Adverse events
United States <sup>10</sup>	67	Median 33 (range: 20–43)	18% < 24 weeks 66% 24–32 weeks 16% > 32 weeks	Median of 9 days (IQR: 7–11)	Obesity (16%), asthma (13%), gestational diabetes (10%) and chronic hypertension (9%)	Median of 8 once-daily doses (IQR: 5–10)	No other investigational therapies were administered	67% admitted to the ICU	93% of pregnant women recovered 1 spontaneous miscarriage at 17/40 gestation in a woman with bacteraemia, infective endocarditis and septic arthritis at the time of having COVID-19 26/67 delivered of which 69% (18/26) were very preterm No maternal or neonatal deaths	33% (22/67) experienced an adverse event 18% (12/67%) experienced a serious adverse event
United States <sup>11</sup>	5	1. 27 2. 39 3. 33 4. 29 5. 41	1. 16 weeks 2. 28 weeks 3. 26 weeks 4. 31 weeks 5. 31 weeks	1. 8 days 2. 12 days 3. 18 days 4. 9 days 5. 8 days	1. Asthma 2. Hypertension, diabetes mellitus 3. Asthma 4. Hypertension, diabetes mellitus, chronic kidney disease 5. None	200 mg loading dose on Day 1 then 100 mg/day for Days 2–10 (or until discharge from hospital)	1. None 2. Hydroxychloroquine 3. Hydroxychloroquine 4. None 5. None	1. No ICU admission 2. Admitted to the ICU 3. Admitted to the ICU 4. No ICU admission 5. No ICU admission	1. Discharged home after an 8-day admission 2. Discharged home after a 19-day admission, uncomplicated Caesarean section during admission at 30-week gestation, infant well 3. Discharged home after a 36-day admission, uncomplicated vaginal delivery during admission at 30-week gestation, infant well 4. Discharged home after a 21-day admission, uncomplicated vaginal delivery during admission at 31 weeks gestation, infant well	1. Mild transient transaminitis after 6 days in view of markedly worsening liver transaminases 2. Mild transient transaminitis 3. Mild transient transaminitis 4. Mild transient transaminitis 5. None reported, had mild transaminitis before remdesivir administration

(Continues)

TABLE 1 (Continued)

Study location	Number of pregnant patients who received remdesivir	Age	Gestation of pregnancy	Duration of symptoms before remdesivir	Comorbidities	Dose/duration of remdesivir	Other SARS-CoV-2/COVID-19 targeted therapies administered	Level of care required	Outcome	Adverse events	
United States <sup>12</sup>	3	1. 25	1. 34 weeks 2. 25 weeks 3. 25 weeks	Not specified (all patients)	1. Intrahepatic cholestasis of pregnancy 2. None reported 3.	200 mg loading dose on Day 1, Day 2 onwards 100 mg/day 1. Received 3 doses 2. Received 8 doses 3. Received 2 doses	None (all patients)	1. Admitted to the ICU	5. Discharged home after a 5-day admission, uncomplicated vaginal delivery 5 weeks after discharge	1. Remdesivir stopped at Day 3 due to transaminitis but further testing indicated pregnancy-associated cholestasis was the cause 2. None reported 3. None reported	
		2. 28									2. Discharged home after a 9-day admission
		3. 29									3. Discharged home after a 6-day admission
United States <sup>13</sup>	1	39	34 weeks	12 days	None	Not specified	Received hydroxychloroquine before remdesivir	Admitted to the ICU	Discharged home after a 9-day admission Made a full recovery and had an uncomplicated delivery at term	Transient mild transaminitis (although unclear if related to remdesivir)	
United States <sup>14</sup>	1	42	26 weeks	1 week	None	200 mg loading dose on day 1 then 100 mg/day for Days 2–10	Dexamethasone, convalescent plasma	Admitted to the ICU	Delivery performed at 29 weeks (by caesarean section) Mother discharged home after a 52-day admission—she continued to require supplemental oxygen and nursing care at home Child (negative for SARS-CoV-2) required neonatal ICU admission—	Probable dexamethasone-associated adrenal insufficiency in child	

TABLE 1 (Continued)

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United States <sup>15</sup>	1	35	36 weeks	Not specified	Asthma, hepatitis C, previous gastrointestinal malignancy, obesity, bipolar disorder	10 days	Convalescent plasma and methylprednisolone	Admitted to the ICU	discharged home on Day 57 of life Vaginal delivery of early-term baby (child tested negative for SARS-CoV-2) Mother discharged to a rehabilitation facility after a 19-day admission	None reported
United States <sup>16</sup>	1	35	22 weeks	10–11 days	Hypertension, type 2 diabetes mellitus, asthma	200 mg loading dose on Day 1 then 100 mg/day for Days 2–5	Tocilizumab	NO ICU admission	Discharged home after a 9-day admission	None reported
United States <sup>17</sup>	1	35	22 weeks	Not specified	Obesity, type 2 diabetes mellitus, asthma	200 mg loading dose on day 1 then 100 mg/day for Days 2–10	Convalescent plasma and hydroxychloroquine	Admitted to the ICU	Discharged home after a 14-day admission No further issues following discharge from hospital at the time of publication	Transient mild transaminitis (although unclear if related to remdesivir)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

There were no deaths among the 67 pregnant patients. However, the study did also report data for an additional 19 mothers who were in the immediate postpartum period, one of whom died. There were no neonatal deaths in this study. Of note, in another US cohort study of 64 hospitalised pregnant women with COVID-19, 25% (16/64) received remdesivir; however, data specifically relating to the remdesivir group were not reported.<sup>3</sup>

Aside from the study by Burckwick and colleagues, published data identified reporting outcomes/adverse events for remdesivir in pregnant women with COVID-19 are limited to one case of five patients, another case series of three patients and five single case reports.<sup>11–17</sup> All 13 patients were hospitalised and 61.5% (8/13) were admitted to the ICU. The high rates of ICU admission (also observed in the study by Burckwick et al.) may, at least in part, be due to potentially lower thresholds for admission in pregnancy-associated COVID-19. Also, the fact that they received remdesivir, for which safety data in pregnancy are scarce, suggests that in certain cases their illness may have been of such severity that the potential benefits were deemed to outweigh the (albeit largely unknown) risks. All 13 patients were in their second or third trimester of pregnancy. In the case series of five pregnant women by McCoy et al., one patient mechanically ventilated pregnant woman at 28-week gestation discontinued remdesivir after six doses due to a worsening transaminitis.<sup>11</sup> Apart from this case and an observed mild transient transaminitis in another 7 of 13 cases, which in one patient was found to be due to pregnancy-related cholestasis and in the other six patients was of unclear aetiology (may have been related to COVID-19 itself [in at least 1 patient the transaminitis was present before remdesivir administration], remdesivir or due to non-COVID-19 complications of pregnancy), there were no identified complications directly attributable to remdesivir. All 13 mothers were discharged from hospital (to their home or for rehabilitation), one child was delivered prematurely that required neonatal ICU admission and three other mothers had uncomplicated preterm deliveries (their infants were well following delivery) but no preterm deliveries were reported in the other nine case reports (4/13, 30.7% delivered preterm). There were no reports of mother-to-child SARS-CoV-2 transmission in any of the 13 cases. Table 1 summarises the published data for remdesivir in pregnancy-associated COVID-19 (studies that did not describe characteristics/outcomes/adverse events specifically for patients receiving remdesivir were not included).

The very limited data available to date do suggest overall that remdesivir is well tolerated in the latter stages (2nd/3rd trimesters) of pregnancy with a low risk of serious adverse events. There is an even greater paucity of data for its use in the first trimester of pregnancy. The anti-COVID-19 armamentarium for all pregnant patients is in dire need of urgent expansion and remdesivir could be a potentially instrumental member; however, further safety and efficacy data are required to support its use.

#### PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/jmv.26986>

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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