Dexamethasone and Remdesivir for the Mitigation of COVID-19 Symptoms in Pregnant Patients

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OBJECTIVE: To report a series that involves the use of dexamethasone and remdesivir to mitigate the effects of COVID-19 in pregnancy.

STUDY DESIGN: Patients in our series had moderate to severe disease and met the criteria for hospitalization. All patients had oxygen saturation <95% and chest CT changes compatible with COVID-19. All patients were treated with remdesivir and dexamethasone after extensive counseling and informed consent by the patient. All patients were also treated with low-molecular-weight heparin, and patients with suspected bacterial pneumonia were treated with ceftriaxone. Our objective was to mitigate the effect of COVID-19 and avoid further decompensation of the maternal-fetal unit.

RESULTS: On average, participants were 27.2 years old, the gestational age was 31.0 weeks, gravidity was 3, and BMI was 31.73. None of the patients had a history of diabetes, chronic hypertension, pulmonary disease, or other comorbidities. The average total hospital stay was 7.2 days (range, 6–10 days).

CONCLUSION: Nine pregnant patients hospitalized with moderate to severe COVID-19 were treated with dexamethasone and remdesivir, the use of which has yet to be established in pregnancy. All patients recovered and none displayed any lasting adverse effects from this treatment. None of the patients required anything other than supplemental oxygen at the beginning of their treatment. Patients with suspected bacterial pneumonia were treated with ceftriaxone and showed a good response. There were no cases of coagulopathy or other complications. (J Reprod Med 2021; 66:321–326)

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Keywords: antiviral agents, coronavirus infections, COVID-19, dexamethasone, pregnancy, remdesivir, SARS-CoV-2.

Coronavirus disease (COVID-19) in pregnancy may cause serious morbidity and mortality in both the mother and the fetus. The COVID-19 pandemic has placed extreme stress on the national health care system and on labor and delivery units throughout the United States and the world. Evolving knowledge of COVID-19 has invoked new ways of managing obstetrical patients. Present management started with no experience by the healthcare teams or based on rigorous data in

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pregnancy in order to develop new therapeutic approaches to mitigate the high morbidity and mortality in our patients. Currently, there are no structured guidelines for the management of COVID-19 and pregnancy. Some data have been published on the use of remdesivir, but these are in the form of case reports.[1] Here we report a series that involves the use of dexamethasone and remdesivir to mitigate the effects of COVID-19 in pregnancy.

Patients in our series had moderate to severe disease and met the criteria for hospitalization.[2] All patients had oxygen (O_2) saturation below 95% and chest CT changes compatible with COVID-19. All patients were treated with remdesivir and dexamethasone after extensive counseling, and written informed consent was obtained from the patient. All patients were also treated with low-molecular-weight heparin, and patients with suspected bacterial pneumonia were treated with ceftriaxone. Our objective was to mitigate the effect of COVID-19 and avoid further decompensation of the maternal-fetal unit.

Materials and Methods

This was a retrospective cohort study conducted at the Las Palmas Medical Center in El Paso, Texas. Our medical center serves metropolitan and outlying areas of El Paso as well as communities from New Mexico that are in close proximity. The study group included patients who tested positive for COVID-19 by polymerase chain reaction (PCR) and had moderate to severe disease as determined by chest CT changes and O_2 saturation below 95%. From September 2020 to January 2021, pregnant patients with COVID-19 who met the criteria for hospitalization according to the published criteria of the Society for Maternal-Fetal Medicine[2] were considered for treatment with remdesivir and dexamethasone. Participants were counseled extensively on the available literature regarding the use of remdesivir and dexamethasone in pregnancy.

All patients also underwent renal function tests. Patients were treated by a multidisciplinary group that included specialists in maternal-fetal medicine, infectious disease, anesthesia, and general OB-GYN. The primary outcome was to mitigate the effects of COVID-19 on the maternal-fetal unit by increasing the O_2 saturation above 95% and stabilizing other parameters such as target organ function. The doses administered to our study group were as follows: remdesivir 200 mg load followed by 100 mg IV daily for 5 days, and dexamethasone 6 mg daily for 5 days. All patients also received prophylactic low-molecular-weight heparin at a weight-based dosage.

Results

The results of this study are summarized in Tables I–II. On average, participants were 27.2 years of age (range, 17–38). The average gestational age

Table I *Admission Data*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age	38	22	18	36	27	17	28	33	26
Gravida	4	3	1	5	3	2	5	4	3
Para	2012	0020	0	4004	1011	1001	4004	2012	1011
Gestational age	36.2	32.1	24.5	29.2	35.7	34.2	25.6	34.7	27.2
Admission O_2 saturation	92	90	93	88	90	89	88	92	91
Maternal BMI	32.0	27.36	37.81	30.01	41.57	21.32	42.50	19.74	33.27
ALT U/L (6–29)	10	29	18	24	12	19	31	14	21
AST U/L (10–30)	14	31	11	28	16	22	40	16	24
D-dimer (2nd trimester: 0.32–1.29 μg/mL) (3rd trimester: 0.13–1.7 μg/mL)	1.30	2.4	1.9	2.1	1.2	1.8	2.8	1.6	1.5
Delivered	Yes	No	No	No	Yes	No	No	No	No
Mode of delivery	VD	—	—	—	CS	—	—	—	—
APGAR score	6/8	—	—	—	4/8	—	—	—	—
Cord pH	7.21	—	—	—	7.08	—	—	—	—
Hospital stay (days)	8	6	6	8	10	7	6	7	7

Table II *Results at Day 5 of Treatment*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
O_2 saturation room air	97	96	96	98	95	99	97	99	98
ALT U/L (6–29)	9	15	17	12	19	14	30	22	11
AST U/L (10–30)	12	23	18	20	21	24	32	17	14
D-dimer (2nd trimester: 0.32–1.29 μg/mL) (3rd trimester: 0.13–1.7 μg/mL)	0.33	0.86	1.02	0.19	0.00	0.74	0.00	1.20	0.95
Antepartum surveillance	Reassuring	Reassuring	Reassuring	Reassuring	Cat II	Reassuring	Reassuring	Reassuring	Reassuring

was 31.0 weeks (range, 24.5–36.2), gravidity was 3 (range, 1–5), and average BMI was 31.73 (average, 27.36–41.57). None of the patients had a history of diabetes, chronic hypertension, pulmonary disease, or other comorbidities.

On admission, all patients had chest CT changes related to COVID-19 including bilateral multifocal infiltrates compatible with viral pneumonia, and 2 had additional evidence of bacterial pneumonia. The average O_2 saturation was 90.3% (range, 88–93%). Five patients had elevated D-dimers (pregnancy parameter range: 1.8–2.8), and 3 had elevated liver function tests (LFTs) (range, 31–40). Two patients were delivered after completion of the treatment (Table I). The first case was decided by the primary obstetrician. The patient's condition had improved and antepartum surveillance was reassuring, and she delivered vaginally without complications. In the second case, the patient was stable but developed a category II strip without improvement, and she was delivered by cesarean section. The newborns were tested for COVID-19 and were both negative.

As shown in Table II, after 5 days of treatment with remdesivir and dexamethasone, the O_2 saturation improved to an average of 97.2% (range, 95–99) at room air. All D-dimers were normal during pregnancy (range, 0.00–1.20). After initial elevation of LFTs (most likely due to treatment with remdesivir), 8 of the 9 patients had normal LFTs 6 days from the start of treatment (ALT range, 9–22; AST range, 12–24), and 1 patient had elevated LFTs until day 8 (average ALT, 30; average AST, 32), at which time the LFTs returned to normal values.

The average total hospital stay was 7.2 days (range, 6–10 days). None of the patients required anything other than supplemental oxygen at the beginning of their treatment. Patients with suspected bacterial pneumonia were treated with ceftriaxone and showed a good response.

There were no cases of coagulopathy or other complications.

Discussion

In this study we describe a total of 9 pregnant patients hospitalized with moderate to severe COVID-19 who were treated with dexamethasone and remdesivir, the use of which has yet to be established in pregnancy. All patients recovered, and none displayed any lasting adverse effects from this treatment.

The Society for Maternal-Fetal Medicine published a severity scale for COVID-19 in pregnancy, as well as criteria for inpatient versus outpatient management,[2] making a point in indicating that management may differ from nonpregnant patients based on oxygen saturation. The Society for Maternal-Fetal Medicine updates the management guidelines for pregnant patients with COVID-19 infections frequently. These can be found at www.smfm.org. The following is the severity scale currently published:

- Asymptomatic or presymptomatic disease or presumptive infection is defined as a positive COVID-19 test result with no symptoms.
- Mild disease is defined as flu-like symptoms, such as fever, cough, myalgias, and anosmia without dyspnea, shortness of breath, or abnormal chest imaging.
- Moderate disease is defined by evidence of lower respiratory tract disease with clinical assessment (dyspnea, pneumonia on imaging, abnormal blood gas results, refractory fever of ≥39.0°C [102.2°F] not alleviated with acetamino-

phen) while maintaining an oxygen saturation of >93% on room air at sea level.
- Severe disease is defined by a respiratory rate >30 breaths per minute (bpm), hypoxia with oxygen saturation ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300, or >50% lung involvement on imaging.
- Critical disease is defined as multiorgan failure or dysfunction, shock, or respiratory failure requiring mechanical ventilation or high-flow nasal cannula.

During normal pregnancy, the risk of bleeding and thrombosis are increased. While bleeding complications mainly occur during or after delivery, the risk of thrombosis is increased throughout pregnancy and is particularly high after delivery.[3] COVID-19 increases the risk of activation of the hemostatic system.[4] Altered rheology, vascular injury, impaired fibrinolysis, and a hypercoagulable state contribute to the increased risk of venous thrombosis. This is also reflected by various alterations of the hemostatic system which occur during normal pregnancy, such as elevated levels of factors VII, VIII, X, and von Willebrand antigen. In addition, we have demonstrated that even uncomplicated pregnancy is accompanied by a substantial hemostatic system activation as indicated by an increase in the plasma concentration of coagulation activation markers, such as prothrombin fragment F1+2 and D-dimer. The elevated levels of D-dimer during pregnancy may reflect increased coagulation activation and thrombin generation, increased fibrinolysis, or a combination of both. Consequently, testing for D-dimer during pregnancy could be useful for the diagnosis and prediction of a venous thromboembolic event or pregnancy-related complications, and for monitoring antithrombotic treatment.[5]

Remdesivir has been used to treat patients with mild to moderate COVID-19, although the data regarding its efficacy remain controversial. Remdesivir has not yet been studied extensively in pregnancy, although ongoing studies are in progress to look at the efficacy and pharmacokinetics of the drug in pregnancy. On October 22, 2020, remdesivir became the first medication approved by the FDA specifically for use in the treatment of SARS-CoV-2 (COVID-19) in adult and pediatric patients who require hospitalization.[7] This approval followed an Emergency Use Authorization (EUA) in May 2020 as a result of its demonstrated efficacy in 3 randomized placebo-controlled trials (RCTs). The first study showed an average median recovery time of 10 days as compared to 15 days in the placebo group ($p<0.001$).[8] A decrease in overall mortality was also seen, although it did not reach the level of statistical significance, and there was no significant difference in adverse events between the 2 groups. The greatest observed clinical benefit was seen in patients on supplemental oxygen as compared to those requiring mechanical ventilation.[8] The second RCT showed a statistically significant improvement in symptoms with a 5-day course of treatment compared to both a 10-day course of treatment and standard of care treatment,[9] whereas the third trial showed no significant difference in efficacy or safety between 5-day and 10-day courses of treatment.[10] Three other randomized clinical trials of remdesivir are currently active or recruiting.[11] However, these studies all excluded pregnant women.

Remdesivir is a nucleoside analogue pro-drug that is converted intracellularly to an active nucleoside triphosphate, *GS-443902*, which inhibits viral replication through RNA-dependent RNA polymerase, which is required for early replication during the infectious cycle.[8,11] It acts on coronaviruses by competing with endogenous nucleotides for incorporation into the virus's replicating RNA, ultimately resulting in termination of the growing RNA chain. *In vitro* studies demonstrated that remdesivir is effective against a SARS-CoV-2 isolate in human airway epithelial cells at a 50% effective concentration (EC50) of 9.9 nM following 48 hours of treatment.[8] Remdesivir has also been shown to have broad-spectrum activity against other coronaviruses (SARS-CoV, MERS-CoV), some filoviruses (Ebola virus, Marburg virus), and paramyxoviruses (respiratory syncytial virus, Nipah virus, and Hendra virus).[8,11]

Standard dosing begins with a 200 mg loading dose, followed by 100 mg per day for at least 5 and no more than 10 days.[12] Remdesivir reaches peak plasma concentration by the end of infusion, regardless of dosage, followed by rapid decline, with a half-life of approximately 1 hour. The plasma protein binding rate of remdesivir is 88% and 2% for its predominant circulating metabolite, *GS-441524*, and it has wide tissue distribution.[8,11] Approximately 74% of the drug is renally excreted, with the majority concentration being *GS-441524*

(49%), followed by remdesivir (10%) and other metabolites.[12]

The most common side effects reported during clinical evaluation included transaminase elevation, headache, nausea, and rash. Less commonly reported adverse effects involved the incidence of hypersensitivity and infusion-related reactions.[7,8,11]

A new study aims to determine how pregnant women metabolize remdesivir and whether there are any potential side effects. IMPAACT 2032 will compare remdesivir use in pregnant and nonpregnant women of reproductive age who are hospitalized with COVID-19. The study will evaluate remdesivir pharmacokinetics in pregnant and nonpregnant women of childbearing age. For women who receive remdesivir within 5 days of delivery, samples from the plasma and umbilical cord will be analyzed for insight into remdesivir pharmacokinetics in the placenta. Breast milk will also be tested for remdesivir. Researchers will document all potential side effects and adverse events (NIH News release, Wednesday, February 17, 2021). A large retrospective study of 86 pregnant and postpartum women with severe COVID-19 who received compassionate use of remdesivir showed that recovery rates were high, with a low rate of serious adverse events. Several of the patients were on mechanical ventilation. In our series, patients were treated early in the course of their disease while experiencing moderate hypoxemia.[1]

In general, the recommended oxygen saturation in pregnancy is 95% or greater. The respiratory changes associated with pregnancy have been well documented and include reductions in functional residual capacity offset by increased minute ventilation. It is also well known that placental O_2 diffusion is dependent on O_2 concentration gradients and placental blood flow. These changes, combined with the respiratory consequences of severe COVID-19 infection, result in the need for higher concentration gradients to prevent fetal asphyxia. Obstetric care providers should target oxygen saturations of 95% or greater during pregnancy to ensure adequate fetal oxygenation. The use of proning, simple nasal cannula, face mask, nonrebreather mask, high-flow nasal cannula, vapotherm, and noninvasive positive pressure delivery systems (i.e., BiPAP) can be utilized to maintain O_2 saturation, often with the assistance of pulmonary or critical care consultants. In this cohort we aggressively sought to avoid these tactics and manage the patients using noninvasive modalities.

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 virus is a major global health threat, with 123,964,077 cases and 2,728,117 deaths confirmed worldwide as of 23 March 2021.[6] The same source reports 383,458,672 positive test results and 543,375 deaths in the United States. The experience in all countries to date has emphasized the intense pressure that a COVID-19 epidemic places on national health systems, with demand for intensive care beds and mechanical ventilators rapidly outstripping their availability, even in relatively highly resourced settings. In the setting of pregnancy, we must weigh the deterioration of the maternal-fetal unit since we have 2 patients in our hands. This has potentially profound consequences for the long-term pregnancy outcome.

Despite these results and those of other investigators, several questions remain to be answered. These include the optimal time to administer remdesivir, the optimal dose of dexamethasone, the optimal duration of both remdesivir and dexamethasone, the pharmacokinetics of remdesivir during pregnancy, and the potential side effects on the fetus. The limitations of this study include the small sample size and long-term follow-up of the infants.

Given the likelihood of worse prognoses for severe COVID-19 cases in the context of pregnancy, coupled with the higher vulnerability of both mother and fetus, mitigation of symptoms and avoidance of preterm delivery is very important to patients, obstetricians, and communities. While we wait for global vaccinations, herd immunity, and other strategies to take effect, we will continue to encounter pregnant patients with COVID-19 and symptoms that endanger the maternal-fetal unit. The results of our pilot study offer a new strategy for treating these cases.

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