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Therapeutic options in the treatment of severe acute respiratory syndrome coronavirus 2 in pregnant patient

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The severe acute respiratory syndrome coronavirus 2 pandemic has resulted in the development of various therapeutics to treat and prevent major complications related to the virus; pregnant patients are vulnerable to acquiring severe acute respiratory syndrome coronavirus 2 because of frequent contact with the healthcare setting. Despite the publication of a plethora of case series and randomized control trials of severe acute respiratory syndrome coronavirus 2 therapeutics, few have addressed treatment in the pregnant population. To date, there has been no published review of therapeutic options in the treatment of pregnant patients with severe acute respiratory syndrome coronavirus 2 infection. Here, we provide a review of available treatments for severe acute respiratory syndrome coronavirus 2, various trials with inclusion and exclusion of the pregnant patients, and potential side effects of each treatment in the pregnant patient.

Key words: anticoagulation, chloroquine, convalescent plasma, corticosteroids, hydroxychloroquine, interleukin-6 inhibitors, lopinavir-ritonavir, remdesivir, severe acute respiratory syndrome coronavirus 2

Introduction

As of July 31, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has infected more than 17 million people worldwide. Several case series have been published with particular attention to incidence and clinical characteristics of pregnant patients with SARS-CoV-2 infection. Thus far, there have been few publications reviewing pharmacologic treatment of SARS-CoV-2 in pregnant patients.

The rapidly changing landscape of pharmacologic therapeutics for the treatment of patients with SARS-CoV-2 infection poses a challenge to physicians managing pregnant patients; this is further amplified in the obstetrics patient who has historically been excluded from clinical trials. Few pregnant patients are enrolled in clinical trials in the treatment of SARS-CoV-2. As such, it is unclear which therapeutic options are available to the pregnant patient and possible side effects of those therapies. We reviewed the literature of therapeutics available for treatment of SARS-CoV-2 in pregnant patients.

Discussion

Following the outbreak in Wuhan, China, of SARS-CoV-2, the pattern of transmission was found to commonly affect patients with older age and chronic comorbidities. Limited data have been published about pregnant women with SARS-CoV-2. In 1 case series by Chen et al,[1] 92% of pregnant patients were found to have mild disease, whereas 8% were noted to have severe disease, defined as the development of hypoxemia; however, none were described as requiring mechanical ventilation. Another case series by Sutton et al[2] found that most pregnant women with SARS-CoV-2 infection were asymptomatic. Neither case series describes whether pharmacologic treatments were offered to pregnant patients for the management of SARS-CoV-2 infection. Data recently published by the Centers for Disease Control suggest that pregnant patients are at a higher risk of admission to the intensive care unit (ICU) and requirement for mechanical ventilation than nonpregnant women.[3]

To date, few randomized clinical controlled trials have been published regarding the effectiveness of pharmacologic treatments for SARS-CoV-2. Pregnant patients have historically been excluded from clinical trials for drugs, and the SARS-CoV-2 has not proven to be an exception.

Treatment options for SARS-CoV-2 have largely been extrapolated from various case series published in the treatment of the Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, which share homology with SARS-CoV-2, and remain investigational. Drugs developed for the treatment of MERS-CoV and SARS-CoV were designed to target various stages in the lifecycle of the novel coronaviruses,[4] but metaanalyses of various therapies in the

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treatment of these viruses found no clear benefit of any specific therapy. Nonetheless, the virulence and adverse consequences of SARS-CoV-2 have led many clinicians to attempt pharmacologic therapies in the attempt to mitigate the impact of the virus. Below is a limited review of direct antivirals and immune modulators and anti-inflammatories commonly proposed to treat SARS-CoV-2 and data regarding use in pregnancy, summarized in Table.

Direct antivirals

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are purported to block viral entry into cells by preventing the glycosylation of host receptors; acidification of the endosome, which limits viral replication; and processing of proteolysis; they are also thought to limit cytokine production.[5] In vitro studies have shown inhibition of SARS-CoV-2 with a half-maximal effective concentration (EC_{50}) of 6.14 μM and 23.90 μM for hydroxychloroquine and chloroquine, respectively.[6] One open-label, nonrandomized clinical trial of hydroxychloroquine compared the outcomes of 20 patients who received hydroxychloroquine and azithromycin (added for synergistic effect) with the outcomes of 16 patients who received no such treatment; they noted that 70% of patients in the treatment arm had virologic clearance compared with 12.5% of patients in the control arm. However, many criticisms have been leveled at this study, including its poor design, the loss of 6 patients from the treatment arm (2 because of admission to the ICU and 1 because the patient died), and the measure of efficacy being viral load instead of a clinical endpoint.[7] Other recently published studies have called into question both the effectiveness and potential harm of these drugs in the treatment of SARS-CoV-2. In a retrospective study by Geleris et al,[8] hydroxychloroquine was neither associated with decreased or increased risk of the primary endpoint of intubation or death (hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.82−1.32); although this study did not demonstrate harm or benefit, the authors concluded that this study did not support the use of hydroxychloroquine in the treatment of SARS-CoV-2. Finally, a randomized clinical trial by Borba et al[9] evaluating the effect of high-dose chloroquine vs low-dose chloroquine in patients hospitalized with SARS-CoV-2 in 81 patients was terminated early because of the high lethality rate (16 of 41 patients [39.0%]) in the group receiving high-dose chloroquine—conjectured secondary to cardiac toxicity and in addition did not demonstrate substantial viral clearance. The aforementioned published studies do not seem to have included pregnant patients; however, hydroxychloroquine has been used in pregnant patients for the treatment of systemic lupus erythematosus. Hydroxychloroquine does cross the placenta, and accumulation in fetal ocular tissues has been observed in animal studies but has not been observed in humans with an otherwise favorable side effect profile in the pregnant patient. Other randomized controlled trials (RCTs) have yet to be published, but hydroxychloroquine and chloroquine have largely fallen out of favor as a treatment for SARS-CoV-2 because of the lack of translation to clinical benefit from in vitro studies and adverse effects, such as QT prolongation with fatal arrhythmia and fulminant hepatic failure, with the Federal Drug Administration (FDA) recently issuing a safety communication against the use of hydroxychloroquine outside the hospital setting or clinical trial.[10]

Lopinavir-ritonavir

Lopinavir-ritonavir is an oral combination agent approved by the FDA for the treatment of HIV that acts by inhibiting type 1 aspartate protease with ritonavir acting to increase plasma half-life. Lopinavir-ritonavir is frequently used as part of a highly active antiretroviral therapy in pregnant women with HIV and has been shown to provide maternal virologic suppression, prevent mother to child transmission, and decrease infant mortality; the drug has been well tolerated in pregnant patients with adverse events reported to include an increase in liver function tests, amylase, and lipase, although there have been reports of preterm delivery ranging from 8.3% to 25%.[11] Its conjectured use in the treatment of SARS-CoV-2 stems from off-label use in the treatment of SARS-CoV-1 and MERS-CoV and in vitro studies suggesting activity against SARS-CoV-1; a systematic review of retrospective studies suggested reduced mortality and intubation rates if the drug was administered early in the onset of disease.[12] Few conclusions could be definitely drawn regarding use of lopinavir and ritonavir in SARS-CoV-1 and MERS-CoV because of the retrospective nature of previously published studies. Recently, a randomized, controlled, open-label trial, including 199 patients to assess the use of lopinavir-ritonavir in the treatment of SARS-CoV-2, demonstrated that it was not superior to standard care nor did treatment result in improved time to clinical improvement (16 days in both treatment and control arms), reduction in mortality at 28 days (19% in the treatment arm and 25% in the control arm), or reduction in viral load at 28 days. A modified intention-to-treat analysis showed a slight clinical improvement by 1 day; however, 14% of the treatment arm were unable to complete treatment because of adverse gastrointestinal events.[13] Furthermore, pregnant patients and patients who were breastfeeding were excluded from this study. Although well tolerated by pregnant patients, lopinavir-ritonavir has also fallen out of favor as a treatment option for SARS-CoV-2 following this publication.

Remdesivir

Remdesivir is an experimental, intravenous novel nucleotide analogue that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication. Initially an investigational drug developed for the treatment of the Ebola virus, it was subsequently shown to have in vitro and in vivo activities (in animal models) against SARS-CoV-1 and MERS-CoV.[14] Remdesivir has also been shown to have an in vitro activity against SARS-CoV-2 with EC_{90} of 1.76 μM.[15] Currently, availability of remdesivir is limited and subject to government-designated supply. Recently, a trial assessing

compassionate use of remdesivir in patients hospitalized in Wuhan with severe SARS-CoV-2 infection (defined as SpO_2 of <94% on room air or requirement for supplemental oxygen) suggested promising outcomes with a total of 61 patients enrolled and 53 patients included in the final analysis. At 28 days of follow-up, clinical improvement was noted in 84% of patients with less improvement noted in those receiving invasive mechanical ventilation (HR for improvement, 0.33; 95% CI, 0.16−0.68). However, 7 of 54 patients (13%) died after completion of treatment. The most serious adverse events reported were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension; furthermore, 12 patients (23%) had serious adverse events, including multiorgan dysfunction syndrome, septic shock, acute kidney injury, and hypotension. Overall, the findings were promising; however, the study was subject to limitations on the basis of the lack of randomized design. Furthermore, most patients were male, and no enrolled patient was pregnant, so little could be extrapolated to the pregnant population from this study.[16] Recently, 2 RCTs regarding use of remdesivir in the treatment of SARS-CoV-2 have been published. The first was a randomized, double-blind, placebo-controlled trial by Wang et al[15] in China enrolling patients with severe SARS-CoV-2 infection, as delineated above; pregnant patients were excluded from this study. The clinical endpoint, time to clinical improvement within 28 days after randomization, was not significantly different between the treatment arm and control arm (median, 21 days vs 23 days; HR, 1.23 [95% CI, 0.87−1.75]) nor was 28-day mortality (14% vs 13%). The treatment arm was noted to have a nonstatistically significant faster time to clinical improvement (median, 18 days vs 23 days; HR, 1.52 [95% CI, 0.95−2.43]). Observed adverse events in the treatment arm included anemia, thrombocytopenia, and increased total bilirubin.[16] The authors of this study attributed the results to the enrollment of a less severely ill study population compared with that of the previously published trial on the compassionate use of remdesivir, inability to reach target enrollment because of the late implementation of treatment in the course of the epidemic in China with fewer cases, and insufficient power to detect differences in clinical outcomes. Although remdesivir was well tolerated in the treatment arm, it did not provide a significant clinical effect.[17] Recently, the randomized, double-blind, placebo-controlled trial, Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial (ACTT), indicated promising results in patients who received remdesivir compared with those who received placebo. In this study of 1063 patients, the study designated time to recovery as the primary outcome with secondary outcomes, including mortality and adverse events. In the final analysis of 1059 patients, time to recovery was at a median of 11 days in the treatment arm vs 15 days in patients who received placebo (rate ratio (RR) for recovery, 1.32; 95% CI, 1.12−1.55; $P<.001$). It should be noted that for those receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at enrollment, the RR for recovery was 0.95 (95% CI, 0.64−1.42). There was no statistically significant difference in the mortality between the treatment arm and the placebo arm (HR, 0.70; 95% CI, 0.47−1.04). Pregnant patients were excluded from this study as well.[18]

Although remdesivir has not shown a mortality benefit, it does seem to have some clinical benefit in shortening the time to recovery, particularly in those requiring supplemental oxygen. Its benefit in patients requiring mechanical ventilation or ECMO is less clear because of the short follow-up period of this study and the protracted illness course of patients with critical illness. The FDA has approved remdesivir in the treatment of SARS-CoV-2.

Despite the exclusion from clinical trials, the manufacturer of remdesivir does allow compassionate use in pregnant patients on a case-by-case basis. At this time, adverse effects in pregnancy and teratogenicity are unknown, although the gastrointestinal side effects may be intolerable for the pregnant patient. In addition, the possibility of hepatic injury by remdesivir in combination with the derangements that occur in SARS-CoV-2 may prove to be difficult in distinguishing from other hepatic complications related to pregnancy, such as acute fatty liver of pregnancy, preeclampsia with severe features, or hemolysis, elevated liver enzymes, and low platelet count, of which all require prompt delivery of the fetus. Compassionate use of this drug should be a risk-benefit discussion among the pregnant patient, her maternal fetal medicine specialist, an infectious disease specialist, and the internist or intensivist; patients should be advised that the safety and efficacy of remdesivir have not been established in pregnancy. Of note, remdesivir is not recommended in patients with an estimated glomerular filtration rate of <30 mL/min.

Convalescent plasma

Convalescent plasma refers to plasma that is collected from individuals following the resolution of infection who have subsequently developed antibodies. Passive antibody therapy via the transfusion of convalescent plasma may decrease clinical severity in individuals with recent infection by clearing both free virus and infected cells. The use of convalescent plasma has previously been used in the treatment of Ebola, SARS-CoV-1, MERS-CoV, and H1N1 influenza A. One systematic review of convalescent plasma in 8 observational studies of more than 700 patients with either SARS-CoV-1 or influenza infection found a reduction in mortality (odds ratio, 0.25 [95% CI, 0.14−0.45]; $I^2=0\%$).[19]

The infusion of convalescent plasma in SARS-CoV-2 infection has not been widely studied; 1 case series of 5 critically ill patients who received 2 transfusions of convalescent plasma in addition to antivirals with methylprednisolone found that viral load declined within days of treatment, acute respiratory distress syndrome resolved, and chest imaging improved, although it should be noted that 2 of 5 patients remained mechanically ventilated at the time of

TABLE

Drugs and their mechanism of action, the number of RCTs, and their safety in pregnancy

Drug name	Mechanism of action	Number of RCTs	Safety in pregnancy
Hydroxychloroquine and chloroquine	- Inhibits preentry step of the viral cycle by interfering with viral particles binding to surface receptor - Interferes with posttranslational modification of viral proteins - Interferes with pH-dependent endosome-mediated viral entry of enveloped viruses, the affecting maturation process - Interferes with cell signaling and regulation of proinflammatory cytokines	- 1 published RCT - 2 pending RCT[a]	Adverse maternal outcomes have not been associated with daily maternal doses $\leq$400 mg/qd[37]
Sarilumab and tocilizumab	IL-6 receptor antagonist that reduces inflammation and mediates a variety of immunologic responses	5 pending RCT[a]	- Crosses the placenta[38] - Increased incidence of preterm birth and spontaneous abortion[39] - Not recommended for treatment of rheumatic diseases during pregnancy[40]
Remdesivir	Inhibition of RNA synthesis	- 2 published RCT - 3 pending RCT[a]	Unknown
Lopinavir and ritonavir	- Binds to the site of HIV-1 protease activity and inhibits the cleavage of protein precursors into individual functional proteins required for infectious HIV - The ritonavir component inhibits the CYP3A metabolism of lopinavir, allowing increased plasma levels of lopinavir	1 published RCT	- Teratogenicity not observed - May have increased risk of preterm delivery, stillbirth, and low birth weight[10]
Convalescent plasma	Neutralizes the virus, preventing further replication and halting ongoing tissue damage	- 5 pending single-arm prospective trials[a] - 1 published RCT - 3 pending RCTs[a]	- Transfusion reaction - Circulatory overload and acute lung injury - Acquisition of blood-borne infections - Potential for alloimmunization
Corticosteroids	Mitigates inflammatory response that results in multiorgan failure	1 published RCT	- Frequently used in pregnancy to promote fetal lung maturity - Increased risk of bacterial and fungal infections - Hyperglycemia - Myopathy

PubMed, National Institutes of Health, ClinicalTrials.gov, the Journal of the American Medical Association, and the New England Journal of Medicine were used to search for completed or pending studies evaluating treatments in pregnant patients diagnosed with severe acute respiratory syndrome coronavirus 2. This table highlights each drug and its mechanism of action, the number of studies identified, and its safety in pregnancy.

CYP3A, cytochrome P450 3A; *IL-6*, interleukin-6; *RCT*, randomized controlled trial.

[a] Clinical trials ongoing in the United States only.

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publication; the primary endpoint was safety (no adverse event was reported).[20] Two other studies of 4 and 10 patients, respectively, suggested an improvement in clinical endpoints, such as discharge from the hospital.[21] These studies are subject to bias given the weak study designs with the lack of control groups, limited power, and confounding treatment with antivirals and steroids. Recently, in an RCT by Li et al of 103 patients in multiple centers across Wuhan, China, the primary outcome of time to clinical improvement within 28 days (defined as being discharged alive or having a reduction of 2 points on a 6-point disease severity scale) was 2.15 days shorter (95% CI, −5.28 to 0.99) in the treatment group compared with the control group. In a subgroup analysis, among patients with severe disease, defined as tachypnea and hypoxia without mechanical ventilation, time to clinical improvement within 28 days was 4.94 days shorter (95% CI, −9.33 to −0.54) in the treatment group compared with the control group. Of note, this benefit was not found in patients with critical illness (ie, those requiring mechanical ventilation or those with multiorgan failure). There was no statistically significant difference between the convalescent plasma group and the control group in any of the major secondary outcomes, including 28-day mortality (15.7% vs 24.0%, respectively; P=.30). The study was underpowered because of being terminated early as the outbreak in Wuhan was near controlled, so definitive conclusions about efficacy could not be established. Finally, pregnant patients were excluded from this study. The trend toward improvement in patients who were severely ill but not critically ill suggests that the administration of treatment early in the course of the disease process rather than later in the disease process may benefit patients.[22] A recent case series of 3 pregnant patients with SARS-CoV-2 infection noted significant clinical improvement in respiratory failure with the administration of convalescent plasma. One patient on supplemental oxygen via nasal cannula was treated with 2 transfusions of convalescent plasma, methylprednisolone, and hydroxychloroquine with resolution of hypoxia and successful pregnancy. The second patient was reported to have severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and was successfully extubated with preservation of the fetus after receiving treatment with convalescent plasma, remdesivir, hydroxychloroquine, and hydrocortisone. The third patient was reported to have severe ARDS requiring ECMO; this patient received convalescent plasma, lopinavir-ritonavir, and ribavirin and survived, although the newborn delivered by cesarean delivery died because of endouterine asphyxiation.[23] Based on the abovementioned literature, convalescent plasma suggests a benefit in shortening the disease duration and possibly in mitigating prolonged respiratory failure, although extrapolation is limited because of various confounding therapies.

Currently, the proposed criteria for potential donors include a history of SARS-CoV-2 infection (confirmed by approved molecular testing), at least 14 days following the resolution of symptoms (ie, fever, cough, shortness of breath), and a negative follow-up molecular test for SARS-CoV-2. Multiple trials are underway for the use of convalescent plasma in the treatment of SARS-CoV-2, some of which do not explicitly exclude pregnant or breastfeeding patients.[24,25] Purported risks are similar to those of transfusion of blood products, including acquisition of other infections like HIV and hepatitis, transfusion-related reactions, transfusion-related acute lung injury and transfusion-related acute circulatory overload, and potential for alloimmunization with risk of hemolytic disease of the fetus and newborn.

Immune modulators and anti-inflammatories

Interleukin-6 inhibitors

SARS-CoV-2 is thought to result in a cytokine storm in some patients through the activation of T lymphocytes and mononuclear macrophages, which produce cytokines, such as interleukin-6 (IL-6), which then bind to IL-6 receptors on target cells; this in turn results in an inflammatory cascade, known as the cytokine storm, in which the immune system becomes dysregulated resulting in vascular hyperpermeability and end-organ damage.[26] Tocilizumab, a recombinant humanized antihuman IL-6 receptor monoclonal antibody, is a drug that is used in the treatment of rheumatoid arthritis and cytokine release syndrome following treatment with chimeric antigen receptor T-cell therapy. It binds to the IL-6 receptor with high affinity, preventing IL-6 and thus attenuating the resultant inflammatory cascade.[27] In addition to tocilizumab, sarilumab is currently in a phase II or III clinical trial as a potential therapy in SARS-CoV-2 infection.[28] Adverse effects of IL-6 inhibitors include increased risk of infection, anaphylaxis, neutropenia, thrombocytopenia, and elevated liver enzymes; ensuring bacterial infection has been ruled out before initiation treatment is paramount as the inhibition of IL-6 could result in the proliferation of previously nascent infection. Pregnant patients are excluded from the RCTs of IL-6 inhibitors; therefore, no conclusion can be drawn about the effectiveness and side effect profile of a therapeutic agent in a pregnant patient with SARS-CoV-2 infection.

Miscellaneous therapies

Corticosteroids

The use of corticosteroids in the treatment of SARS-CoV-2 is conjectured to mitigate the widespread inflammatory response that results in multiorgan failure. During the early months of the pandemic, corticosteroid use in the treatment of SARS-CoV-2 was linked to increased morbidity and mortality in patients, conjectured because of the decreased clearance of viral RNA from the blood and the respiratory tract.[29] In pregnancy, corticosteroids are commonly given for fetal lung maturity in the event of premature delivery (between 23 and 36 weeks of gestation); however, dosing for fetal lung maturity is only a fraction of the dosing that was reportedly used in patients with SARS-CoV-2 infection.[30] Recently, the open-label, Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial assessed the use of

dexamethasone in patients diagnosed with SARS-CoV-2 infection. This trial was remarkable for its inclusion of pregnant patients. In the protocol of the treatment arm, patients received dexamethasone 6 mg orally or intravenously daily for 10 days; pregnant or breastfeeding women in the treatment arm instead received prednisolone 40 mg orally or hydrocortisone 80 mg intravenously twice daily for 10 days. Overall, 6425 patients were included in the study, with 2104 randomized to the treatment arm. Six pregnant patients were included in this study, although their individual outcomes are not known. In addition, 28-day mortality was lower in the treatment arm compared with the group that received usual care (22.9% vs 25.7%; $P<.0001$). The incidence of death was notably lower in patients receiving supplemental oxygen via nasal cannula, high-flow nasal cannula, or noninvasive ventilation (23.3% vs 26.2%; RR, 0.82; 95% CI, 0.72−0.94) and in those receiving invasive mechanical ventilation (29.3% vs 41.4%; RR, 0.64; 95% CI, 0.51−0.81). In contrast, patients who did not require supplemental oxygen had no clear mortality benefit with corticosteroid use (17.8% vs 14.0%; RR, 1.19; 95% CI, 0.91−1.55). Finally, the risk of progression to invasive mechanical ventilation was lower in the treatment arm (risk ratio, 0.77; 95% CI, 0.62−0.95).[31] The limitations of this study include the lack of standardization of the usual care arm because of rapidly evolving treatments and the lack of follow-up beyond 28 days. Based on the preliminary results of the RECOVERY trial, corticosteroids can be a safe and cost-effective treatment option for pregnant patients who develop respiratory failure requiring supplemental oxygen or invasive mechanical ventilation. Adverse effects of corticosteroids that should be considered include hyperglycemia with resultant intrauterine fetal growth restriction, increased risk of bacterial and fungal infections, and steroid-induced myopathy, which may further be compounded by the use of paralytic drips in the treatment of severe ARDS.

Anticoagulation

In patients who develop sepsis from various infections, derangements in the coagulation pathway can occur and are associated with poor outcomes. In SARS-CoV-2, the stipulation for hypercoagulability stems from endothelial dysfunction with subsequent increased risk of venous thromboembolism.[32] There have also been case reports of antiphospholipid antibody development in SARS-CoV-2 infection, which places patients at a higher risk of thrombosis.[33] Given the prothrombotic state induced by SARS-CoV-2, the International Society on Thrombosis and Haemostasis recommends that low-molecular-weight heparin (LMWH) be administered in the absence of any contraindications (active bleeding and platelet count less than 25×109/L) in severe SARS-CoV-2 infection.[34] The recommendation follows a metaanalysis by Tang et al[35] of 449 patients with severe SARS-CoV-2 infection in which patients with sepsis-induced coagulopathy score of ≥4 had a reduction in mortality with the prophylactic dose of LMWH (40.0% vs 64.2%; $P=.029$) and in those with a D-dimer level of >6 times the upper limit of normal (32.8% vs 52.4%; $P=.017$). In pregnant patients, inflammatory illness increases the risk of preterm birth and also places the pregnant patient at an elevated risk of peripartum bleeding, which may be worsened by therapeutic anticoagulation. Nonetheless, pregnancy itself induces a prothrombotic state, and therefore, prophylactic anticoagulation with LMWH should be strongly considered and its dose possibly doubled in the case of severe SARS-CoV-2 infections.[34,36]

Conclusion

There are few case studies of SARS-CoV-2 therapeutics in pregnant patients and few ongoing RCTs, including pregnant patients that provide guidance on the choice of therapeutic. Published case series and trials thus far should be interpreted with caution given few trials have been adequately powered for clinical outcomes, are subject to selection bias, and include other treatments given to patients that could confound findings. Use of the above-listed antivirals or immune modulators in patients should be done as part of a clinical trial, but this poses a difficulty in the pregnant population who is often excluded from clinical trials. Based on our review, agents that can be provided to the pregnant patient include corticosteroids, remdesivir, and convalescent plasma; however, the side effect profile of any therapeutic agent has not been fully established in the pregnant patient. The initiation of any pharmacotherapy for the treatment of SARS-CoV-2 must be a comprehensive and multidisciplinary risk-benefit discussion between the pregnant patient and her physicians. ■

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