Management of Acute Severe Ulcerative Colitis in a Pregnant Woman With COVID-19 Infection: A Case Report and Review of the Literature

Melissa H. Rosen, MD, Jordan Axelrad, MD, MPH,* David Hudesman, MD,* David T. Rubin, MD,†,● and Shannon Chang, MD**

First detected in Wuhan, China, the novel 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA beta-coronavirus responsible for an unprecedented, worldwide pandemic caused by COVID-19. Optimal management of immunosuppression in inflammatory bowel disease (IBD) patients with COVID-19 infection currently is based on expert opinion, given the novelty of the infection and the corresponding lack of high-level evidence in patients with immune-mediated conditions. There are limited data regarding IBD patients with COVID-19 and no data regarding early pregnancy in the era of COVID-19. This article describes a patient with acute severe ulcerative colitis (UC) during her first trimester of pregnancy who also has COVID-19. The case presentation is followed by a review of the literature to date on COVID-19 in regard to inflammatory bowel disease and pregnancy, respectively.

Key Words: ulcerative colitis, inflammatory bowel disease, pregnancy, coronavirus, COVID-19, cyclosporine

INTRODUCTION

First detected in Wuhan, China, the novel 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA beta-coronavirus responsible for an unprecedented, worldwide pandemic caused by COVID-19. Optimal management of immunosuppression in inflammatory bowel disease (IBD) patients with COVID-19 infection currently is based on expert opinion, given the novelty of the infection and the corresponding lack of high-level evidence in patients with immune-mediated conditions. There are limited data regarding IBD patients with COVID-19 and no data regarding early pregnancy in the era of COVID-19. We present a patient with acute severe ulcerative colitis (UC) during her first trimester of pregnancy and who also has COVID-19.

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From the *Division of Gastroenterology and Hepatology, NYU Langone Health, New York, NY; †University of Chicago Medicine Inflammatory Bowel Disease Center, Chicago, IL

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Address correspondence to: Melissa H. Rosen, MD, NYU Langone Health Joan H. Tisch Center for Women's Health, 207 East 84th Street, New York, NY 10028, USA. E-mail: melissa.rosen@nyulangone.org.

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CASE REPORT

A 26-year-old female resident of Brooklyn, New York, with a history of ulcerative pancolitis was hospitalized with abdominal pain, diarrhea, hematochezia, and urgency in the setting of a UC flare. Shortly after her diagnosis of UC at 14 years of age, she received 3 infliximab induction doses and went into clinical remission. She then transitioned to 6-mercaptopurine and mesalamine therapy without further infliximab maintenance therapy. By age 20, the patient had self-discontinued her UC medications and remained off medications and in clinical remission. Her current symptoms started 6 weeks before hospitalization.

Upon admission, her laboratory values were notable for a C-reactive protein (CRP) of 166 mg/L (0–5 mg/L). She was found to have a positive urine pregnancy test on admission, confirmed by an elevated serum beta-human chorionic gonadotropin (beta-hCG) level. Due to irregular menstrual cycles, the patient was unclear of the date of her last menstrual period. This was presumed to be a very early pregnancy as a transvaginal ultrasound at admission did not reveal an intrauterine pregnancy, making it difficult to determine the gestational age. Stool studies were negative for standard pathogens, including *Clostridioides difficile*. A flexible sigmoidoscopy revealed Mayo 3 proctitis. Due to the severity of inflammation, the sigmoidoscopy was not continued beyond this point. Biopsies confirmed moderately to severely active chronic inflammation. Cytomegalovirus was not identified with immunohistochemistry. She received intravenous methylprednisolone and improved clinically. As the patient was improving on steroids and given the rapidly increasing rate of COVID-19 infected patients at our institution, the decision was made to discharge the patient home on an oral prednisone taper on hospital day 5 with plans to start infliximab as an outpatient.

C-reactive protein had decreased to 33 mg/L on the day of discharge.

Two days later, she returned to the emergency department due to worsening bloody diarrhea and abdominal pain. Her CRP had increased from 33 mg/L to 100 mg/L. She denied any fever, cough, or shortness of breath, but given her elevated CRP, diarrhea, and repeat admission, RT-PCR testing for SARS-CoV-2 by nasopharyngeal swab was performed and was positive. A transvaginal ultrasound was repeated, and a fetal heartbeat with a yolk sac was identified, confirming an early intrauterine pregnancy, and maternal fetal medicine joined her care team. She resumed intravenous methylprednisolone and had some reduction of bowel frequency with a concurrent decrease in CRP. Nonetheless, when she was transitioned to oral prednisone, her abdominal pain recurred, and her CRP rose again. On day 5 of her readmission, she developed pleuritic chest pain. Electrocardiogram, troponins, D-dimer, and chest x-ray were unremarkable. Given concern for progressive COVID-19 symptomatology with her chest discomfort, the patient was started on azithromycin and hydroxychloroquine. Due to her inability to transition to oral prednisone successfully, intravenous cyclosporine was initiated at 2 mg/kg continuous infusion. The patient's UC symptoms and CRP gradually improved on cyclosporine, with goal morning levels between 200 and 400 ng/mL.[1] Unfortunately, on day 9 of this hospitalization, she developed vaginal bleeding, a reduced beta-hCG, and experienced a spontaneous abortion. The patient was discharged home on day 11 on cyclosporine, prednisone, and a plan for outpatient infliximab initiation.

IBD, PREGNANCY, AND COVID-19: A REVIEW OF THE LITERATURE

Guidelines for the management of IBD during pregnancy are well established,[2] but the optimal treatment for UC during pregnancy and concomitant COVID-19 is not known.

Although intravenous steroids are the mainstay of treatment for acute severe UC in the hospitalized patient, the use of steroids in the first trimester of pregnancy may be associated with a risk of cleft lip or cleft palate.[3] However, the risk of cleft lip and palate has only been associated with dermatologic steroid exposure during the first trimester, not with intravenous or oral steroid exposure.[4] Data from respiratory syncytial virus (RSV) in children and experience from the prior coronavirus outbreaks, severe acute respiratory syndrome (SARS) in 2003, and Middle East respiratory syndrome (MERS) in 2012 demonstrated no benefit of high dose corticosteroids for the acute respiratory distress syndrome and possibly a reduction in viral clearance.[5–7] The recommendations for steroid use in COVID-19 are mixed; some reports advise steroid avoidance when possible[8] or tapering the dose to an equivalent of less than 20 milligrams daily of prednisone.[9]

In steroid-refractory patients, the treatment for acute severe UC is typically either infliximab or cyclosporine.[10] Because of our patient's infection with the SARS-CoV-2 virus and the potential for development of progressive COVID-19, cyclosporine was chosen as salvage therapy, given cyclosporine's shorter half-life when compared with the longer half-life of infliximab. Moreover, intriguing research stemming from the 2003 SARS outbreak supports the use of cyclosporine A in the setting of coronavirus infection. In 2011, de Wilde and colleagues published an in vitro study demonstrating that cyclosporine A inhibited coronavirus replication.[11] Although the exact mechanism of inhibition of coronavirus replication is yet to be elucidated, these findings provide an additional advantage that cyclosporine may confer over infliximab in the setting of acute severe ulcerative colitis complicated by COVID-19.

There are limited data regarding cyclosporine use during pregnancy. According to the American Gastroenterological Association's Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway, cyclosporine is acknowledged to have limited data in pregnancy, yet it can be used as a salvage therapy. Cyclosporine crosses the placenta, and it may be detected in newborn serum for several days after birth.[12] The majority of data regarding cyclosporine safety during pregnancy originates from the organ transplant population. Cyclosporine use during pregnancy has been associated with hypertension, gestational diabetes, preterm birth, and low birthweight. A retrospective study of 629 pregnancies in renal transplant patients with cyclosporine exposure during pregnancy from 6 weeks gestation reported rates of 9.7% for fetal loss and 3% for congenital malformations, which are similar to those of the general population.[13]

Tumor necrosis factor alpha (TNFα) is a ubiquitous cytokine associated with both infectious and inflammatory disorders and has a clear role in the pathogenesis of both IBD and the inflammatory phase of lung disease in patients with COVID-19.[14] Given the increase in TNFα production associated with severe COVID-19, it is hypothesized that anti-TNFα therapy may mitigate the cytokine release syndrome. Clinical trials are underway to evaluate the use of anti-TNFα and other anticytokine therapies in the treatment of COVID-19.[15] The safety profile of anti-TNFα therapy during pregnancy is well established.[14]

Recommendations regarding IBD management in the setting of COVID-19 infection are evolving. The necessity for guidance was addressed by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) in their publication, "Management of Patients with Crohn's Disease and Ulcerative Colitis During the COVID-19 Pandemic: Results of an International Meeting."[9] The recommendation is to continue biologic therapy in the absence of SARS-CoV-2 infection. However, in patients with COVID-19, the severity of the IBD must be taken into account, and treatment of the IBD must be balanced with the severity of the COVID-19.

There is a potential risk of vertical transmission from pregnant mothers to their newborns, as the angiotensin

converting enzyme 2 (ACE-2) receptor, which functions as the putative receptor for SARS-CoV-2, is expressed in the placenta.[16] In Wuhan Children's Hospital, of the 33 neonates born to COVID-19 mothers, 3 neonates were found to be COVID-19 positive, although it was postulated that these infections may have been from postnatal exposure to the mothers, caregivers, or other infected health care providers. These 3 neonates had mild disease courses and favorable outcomes. The study suggested testing all fluids (fecal, amniotic, cord blood, and breast milk) for COVID-19.[17] In another study of 38 pregnant women with COVID-19, there were no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their neonates, as all neonatal specimens tested negative for the virus.[18–21] Finally, at Zhongnan Hospital of Wuhan University, 6 infants born to mothers with confirmed COVID-19 tested negative by serum or throat swab for COVID-19 but were noted to have virus-specific antibodies in serum samples.[22]

Limited data regarding COVID-19 and pregnancy outcomes have been reported for pregnant women in their second or third trimester. In a cohort of 118 pregnant women in Wuhan, China, the most common presenting symptoms of COVID-19 were fever (75%), cough (73%), chest tightness (18%), and fatigue (17%).[23] Of the 68 women who gave birth by the time of publication, 63 (93%) underwent cesarean section, with the indication for 61% of these cases being "due to concerns about COVID-19." Median Apgar scores were 9 (interquartile range 8–9). There were no neonatal deaths. In a series of 55 pregnant women with COVID-19, it was found that fetal complications of COVID-19 included miscarriage (2%), intrauterine growth restriction (10%), and preterm birth (39%).[24]

In summary, we present a case of acute severe UC in a first-trimester pregnant patient with COVID-19 infection. The pregnancy unfortunately resulted in spontaneous abortion. It is unknown whether her severe UC, her concurrent COVID-19 infection, genetic abnormalities, or a combination of factors were the cause of the spontaneous abortion. Uncontrolled, severe UC can increase the likelihood of adverse birth outcomes.[25] Given the novelty of the SARS-CoV-2 virus, there is little data on perinatal outcomes in mothers who acquire COVID-19 during the first trimester. However, a recent systematic review and meta-analysis of coronavirus infections (SARS, MERS, and COVID-19) found a miscarriage rate of 39%, which is higher than the rate seen in the general population.[26] Unfortunately, the products of conception were not able to be tested for COVID-19 or fetal abnormalities in this case. The long-term overall impact to the fetus in the setting of COVID-19 infection in the mother during the first trimester is not yet known.

The optimal management of IBD in pregnancy during the COVID-19 pandemic has yet to be defined. Restricting or limiting the use of steroids is recommended. The use of infliximab or cyclosporine may be considered for salvage therapy, but the risks and benefits must be carefully considered on a case-by-case basis. Multidisciplinary management with maternal fetal medicine, infectious disease, gastroenterology, and colorectal surgery is recommended.

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