Article published online: 2024-01-23

Intrahepatic Cholestasis of Pregnancy and Transaminitis in Women with COVID-19: A Case Series

Anne R. Waldrop, MD[1] Andrea Henkel, MD[1] Kelley B. Lee, MSN, WHNP[1] Maurice L. Druzin, MD[1] Natali Aziz, MD, MS[1] Yasser El-Sayed, MD[1] Deirdre J. Lyell, MD[1]

[1] Department of Obstetrics and Gynecology, Stanford University, Stanford, California

Address for correspondence Anne R. Waldrop, MD, Department of Obstetrics and Gynecology, Stanford University, 300 Pasteur Drive, Room HG332, Stanford, CA 94305 (e-mail: awaldrop@stanford.edu).

AJP Rep 2024;14:e16–e18.

Abstract

Objective The four initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected pregnant women presenting at term gestation to our institution presented with transaminitis. Three of the four were diagnosed with intrahepatic cholestasis of pregnancy (IHCP). Growing evidence exists of an associated transaminitis in nonpregnant SARS-CoV-2 patients. However, there are limited data of hepatic involvement of SARS-CoV-2 in pregnancy, and no previous studies have assessed the association with IHCP in patients with coronavirus disease 2019 (COVID-19).

Study Design This was a retrospective, single-center case series of four consecutive pregnant women with a positive result for SARS-CoV-2 presenting with transaminitis in third trimester.

Results The clinical courses of four pregnant women with COVID-19 and transaminitis, three of four of whom were diagnosed with IHCP, are described. Testing for SARS-CoV-2 was done through a reverse transcription polymerase chain reaction test of a nasopharyngeal swab.

Conclusion As we await larger studies ascertaining the incidence of IHCP in SARS-CoV-2, this prevalence highlights the importance of diagnosing IHCP among women with COVID-19 as a potential etiology of transaminitis, as IHCP risks may be ameliorated with earlier delivery. Moreover, delineating a hepatobiliary association in pregnancy may provide further information about the mechanism of liver impairment in SARS-CoV-2 in all patients.

Keywords
- COVID-19
- IHCP
- intrahepatic cholestasis of pregnancy
- maternal
- novel coronavirus
- SARS-CoV-2
- transaminitis

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has caused an unprecedented pandemic and ongoing global health emergency. As of November 2020, there have been more than 53 million global confirmed cases.[1] Despite the rapid spread of the disease, data are limited on its implications for pregnancy. A recently published expert review entitled "Labor and Delivery Guidance for COVID-19" notes that patients with SARS-CoV-2 may develop transaminitis which should be considered among women undergoing evaluation for preeclampsia.[2] We present a case series of four consecutive full-term pregnant women who presented from April 11, 2020, to

received
August 15, 2020
accepted after revision
October 22, 2023

DOI https://doi.org/10.1055/s-0043-1777999.
ISSN 2157-6998.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

May 9, 2020, with SARS-CoV-2 and transaminitis, three of whom were diagnosed with intrahepatic cholestasis of pregnancy (IHCP). This represents 4 out of the 11 (4 term and 7 preterm) SARS-CoV-2-infected pregnant patients requiring admission at our institution at the time of report submission. IHCP is relatively uncommon, with an incidence of 5.6% reported in a population similar to ours,[3] and any relationship between IHCP and SARS-CoV-2 has not previously been described.

Study Design

This was a retrospective, single-center case series of four consecutive pregnant women who had a positive result for SARS-CoV-2 testing and presented with transaminitis in the third trimester.

Results

The clinical courses of four pregnant women with COVID-19, all with transaminitis, three of four of whom were diagnosed with IHCP, are described later. Testing for the presence of SARS-CoV-2 was done through a reverse transcription polymerase chain reaction (RT-PCR) test of a nasopharyngeal swab.

Case 1

A 26-year-old gravida 1, para 0 Hispanic female at $37^{0/7}$ weeks' gestation presented to our labor and delivery unit for scheduled induction of labor due to IHCP, where she reported sore throat and "allergies." She was tested for SARS-CoV-2 by nasopharyngeal swab RT-PCR and found to be positive. Four days prior, she had presented to her obstetrics provider with new-onset palmar pruritus. Serum bile acids were drawn and ursodiol was empirically initiated. On presentation to labor and delivery unit, bile acids were 42 µmol/L ($\leq$ 10 µ mol/L), aspartate transaminase (AST) was 131 U/L, and alanine transaminase (ALT) was 134 U/L. Her hepatitis B and C viral studies were negative.

She developed preeclampsia with severe features during her intrapartum course, based on blood pressures of 175/111 and 166/101, a mild headache, and an elevated protein-to-creatinine ratio of 0.36. Her oxygen saturation and pulmonary examination remained normal. She received 20 mg of intravenous labetalol for blood pressure control and intravenous magnesium sulfate, with a 4-g bolus followed by a continuous infusion of 2 g/h for seizure prophylaxis.

She progressed to 10 cm cervical dilation, pushed for 120 minutes with a category 2 fetal heart tracing, and subsequently underwent an uncomplicated forceps-assisted vaginal delivery for fetal indication and maternal exhaustion. Following delivery, her blood pressures remained in the nonsevere range (less than 160/110 mm Hg), and intravenous magnesium sulfate therapy at a maintenance rate of 2 g/h was continued for 24 hours. The patient was discharged home on postpartum day 2 at which point her sore throat had resolved.

Case 2

A 25-year-old gravida 3, para 2 Hispanic female at $34^{2/7}$ weeks' gestation presented to the emergency department with a 10-day history of intermittent fevers and myalgias and tested positive for SARS-CoV-2 by nasopharyngeal swab RT-PCR. At presentation, her temperature was 103°F, heart rate ranged from 130 to 150 beats per minute, respiratory rate was 30 to 40 breaths per minute with notable abdominal accessory muscle use, and oxygen saturation was greater than 96% with 1 to 3 L/min of oxygen via nasal cannula. The fetal heart rate was tachycardic, in the 160 to 170 beats per minute. Chest radiograph was notable for patchy bilateral consolidations, consistent with previously described findings in COVID-19.

She was admitted to the intensive care unit for acute hypoxic respiratory failure. Hydroxychloroquine was initiated while awaiting approval for compassionate use of remdesivir, which was ultimately initiated on hospital day 3. On hospital day 6, she was noted to have a new-onset transaminitis with AST 681 U/L and ALT 420 U/L. Remdesivir was discontinued due to the transaminitis, and evaluation for obstetric etiologies of transaminitis was initiated. A hepatitis panel was negative, and a right upper quadrant ultrasound was unremarkable. The patient developed pruritis in the palmar and dorsal surfaces of her hands. Bile acids resulted as 158 µmol/L consistent with IHCP, and ursodiol therapy was initiated. She was discharged on hospital day 8, at $35^{1/7}$ weeks when respiratory symptoms improved.

She was later readmitted for induction of labor at $37^{2/7}$ weeks' gestation due to IHCP. Her transaminitis had resolved by the time of admission and repeat testing for SARS-CoV-2 at admission was negative by RT-PCR. She had an uncomplicated vaginal delivery.

Case 3

A 45-year-old gravida 2, para 1 Hispanic female at $37^{3/7}$ weeks' gestation with a history of cholecystectomy presented for induction of labor for newly diagnosed IHPC. She was tested for SARS-CoV-2 per our universal screening process, which was initiated on our labor and delivery unit at the end of April 2020. She tested positive for SARS-CoV-2 by nasopharyngeal swab RT-PCR. She was asymptomatic for SARS-CoV-2 and denied recent sick contacts. The day prior to presentation, she was seen in her obstetrics clinic and reported new full body pruritus. First-trimester prenatal laboratories were negative for hepatitis B and C viruses. Bile acids resulted at 49 µmol/L, and liver enzymes were AST 188 U/L and ALT 279 U/L; therefore, delivery was recommended.

On presentation to our labor and delivery unit, the patient's blood pressures were 140/90 and her protein-to-creatinine ratio was elevated at 0.9, consistent with preeclampsia without severe features. She underwent an uncomplicated repeat cesarean delivery after declining a trial of labor after prior cesarean section. She was discharged on postpartum day 4 with normal to mild range elevated blood pressures, and a decreasing transaminitis.

Case 4

A 29-year-old gravida 3, para 1 Hispanic female at $39^{0/7}$ weeks' gestation presented 2 days prior to a scheduled repeat cesarean delivery for routine preprocedure SARS-CoV-2 testing where she tested positive. She was asymptomatic and was admitted to labor and delivery unit where she underwent an uncomplicated repeat cesarean delivery. Her admission laboratory testing revealed a transaminitis peaking at AST 60 U/L and ALT 45 U/L. She remained normotensive; therefore, the transaminitis was trended during her admission without further evaluation. Prenatal laboratories in the first trimester were negative for hepatitis B and C viruses. There is no documentation regarding pruritis symptoms in her medical record. She was discharged on postoperative day 4 without respiratory symptoms.

Conclusion

Data about SARS-CoV-2 in pregnancy are limited. It is currently unknown if the rate of IHCP is elevated in women with COVID-19. However, a degree of liver dysfunction appears to be common in patients with SARS-CoV-2 infection.[4] In the largest cohort of nonpregnant patients ($n = 1{,}099$) with laboratory-confirmed SARS-CoV-2 from 552 hospitals in 30 provinces in China, 21% (158/754) presented with ALT more than 40 U/L and 22.2% (168/754) with AST more than 40 U/L.[5] In one of the first case series of pregnant women out of Wuhan, China, two of seven (29%) pregnant women had differing degrees of liver function abnormalities.[6]

Underlying chronic liver diseases, such as hepatitis C and nonalcoholic liver cirrhosis predispose women to developing higher rates of IHCP.[7] This adds to the biologic plausibility that liver dysfunction with SARS-CoV-2 may be related to IHCP found in pregnant patients.

In a randomized, double-blind, placebo-controlled, multicenter trial of remdesivir for severe SARS-CoV-2 infection, Wang et al found that patients randomized to remdesivir were more likely to have an increased AST and the need to discontinue the drug compared with placebo.[8] Thus, the antiviral treatment for SARS-CoV-2 infection may also predispose women to liver dysfunction. Notably, pregnant women were excluded from this study. This case series includes four Hispanic women. The baseline incidence of IHCP for Hispanic women is approximately 5.6%, as described in a primarily Hispanic population in Los Angeles.[3] Interestingly, of the four women initially diagnosed with COVID-19 who presented at term gestation at our institution, all were noted to have transaminitis, and three-quarters were diagnosed with IHCP.

We recognize that this case series represents a small sample of the overall number of SARS-CoV-2 in pregnancy. Our observation of the high prevalence of IHCP in our patient cohort may ultimately prove to be a coincidence when larger cohort studies become available, and larger studies are needed to examine this possible association. Additionally, perinatal outcomes for cases of IHCP which occur in the setting of COVID-19 require further investigation and may differ from those known outcomes identified in cases of spontaneous IHCP. As we await larger cohort studies to ascertain the rate of IHCP and transaminitis associated with SARS-CoV-2 infection, this strikingly high proportion underscores the importance of assessing for IHCP among women with COVID-19 as a potential associated etiology of transaminitis, given IHCP poses a risk of stillbirth that may be ameliorated with early delivery. Moreover, delineating a hepatobiliary association in pregnancy may also provide additional information about the mechanism of liver impairment in nonpregnant patients infected with SARS-CoV-2.

Funding
None.

Conflict of Interest
None declared.

Acknowledgments
The authors of the manuscript thank the countless nurses, resident physicians, maternal–fetal medicine attendings, anesthesiologists, and critical care fellows and attendants who cared for these patients and continue to care for our patients in a multidisciplinary fashion.

References

1 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(05): 533–534
2 Boelig RC, Manuck T, Oliver EA, et al. Labor and delivery guidance for COVID-19. Am J Obstet Gynecol MFM 2020;2(02):100110
3 Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. J Perinatol 2006;26(09):527–532
4 Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. Clin Gastroenterol Hepatol 2020;18(07):1561–1566
5 Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720
6 Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis 2020;20(05):559–564
7 Ropponen A, Sund R, Riikonen S, Ylikorkala O, Aittomäki K. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology 2006;43(04):723–728
8 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–1578