



COVID-19 and HELLP: Overlapping Clinical Pictures in Two Gravid Patients

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Abstract

Background The impact of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) on pregnancies is currently under investigation. There is a significant overlap between the clinical findings in novel coronavirus disease 2019 (COVID-19) and hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP).

Cases Patients presented at 22 and 29 weeks of gestation with suspected COVID-19 pneumonia. While the patient at 22 weeks of gestation subsequently had an intrauterine fetal demise, the patient at 29 weeks of gestation delivered via an emergency cesarean delivery for nonreassuring fetal status. Both patients also developed transaminitis, thrombocytopenia, and disseminated intravascular coagulation with a proof of hemolysis on peripheral smear.

Conclusion Clinicians are encouraged to consider both of these diagnoses when caring for pregnant women during the COVID-19 pandemic to assure that both maternal and fetal concerns are addressed and treated appropriately.

Keywords

- ▶ COVID-19
- ▶ HELLP
- ▶ pregnancy
- ▶ overlapping conditions

During the current novel coronavirus disease 2019 (COVID-19) pandemic, clinicians from every field are encountering novel findings. There have been reports of infectious diseases mimicking hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP) in gravid patients.^{1,2} However, our understanding of how severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) affects these patients has not been elucidated. These findings can become clinical conundrums when there is significant overlap with known, and serious, syndromes in pregnancy. This case series describes two gravid patients who tested positive for the novel coronavirus and had laboratory findings that mimicked HELLP.

HELLP is generally characterized by three diagnostic criteria: microangiopathic hemolysis with schistocytes on peripheral blood smear, elevated liver enzymes, and thrombocytopenia.³ While HELLP is typically associated with proteinuria and hypertension, representing a severe form of preeclampsia, atypical presentations of HELLP have been described in the literature.^{4,5} Laboratory abnormalities commonly seen in COVID-19 patients include lymphopenia, leukopenia, and elevated liver enzymes.⁶

Additionally, studies of patients with severe disease have shown laboratory abnormalities consistent with disseminated intravascular coagulation (DIC), including an elevated D-dimer and evidence of microangiopathic hemolytic anemia.⁶ In small studies of pregnant women with COVID-19, laboratory abnormalities were similar and included elevated C-reactive protein (CRP), lymphopenia, and elevated liver enzymes.⁷

Cases

The first patient was a 41-year-old G9P8008, with no previous medical history, who was admitted for suspected COVID-19 pneumonia at 22 weeks of gestational age. Consistent with other cases already reported in the literature, the patient decided to seek medical care on COVID-19 at day 7 and reported 1 week of worsening fever, cough, and chest pain, and had no obstetrical complaints. Her physical exam was remarkable for mild respiratory distress with mild crackles appreciated bilaterally on lung examination. Chest X-ray was performed with an abdominal shield, which

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showed diffuse hazy and patchy opacities of the bilateral lungs with a basilar and peripheral predominance. The constellation of these findings was highly suspicious for atypical/viral pneumonia (COVID-19). She was normotensive with a blood pressure range of 92 to 106/50 to 64. Urinalysis on admission was unremarkable with +1 protein. Nasopharyngeal testing performed on the day of admission for the novel coronavirus was subsequently positive. Given the fact that the patient was previable, a bedside transabdominal ultrasound was not performed and there is no estimated fetal weight documented in chart. The decision of not performing a bedside ultrasound was in attempt to limit provider's prolonged exposure time to patients with suspected COVID-19 infection. Bedside Doppler examinations were performed and a positive fetal heart rate of 150 beats per minute (bpm) was documented. A fetal heart rate check was performed daily. She received hydroxychloroquine, azithromycin, and ceftriaxone. Her oxygen saturation remained between 88 to 92% on 100% nonrebreather. A ventilator was not used at this time, and therefore, no FIO₂ was documented. Arterial blood gas performed at that time showed the following findings: pH, 7.430/PaCO₂, 31/PaO₂, 285/bicarb, 20.6/base excess of -2.8. On hospital day 5, COVID-19 day 12, she was diagnosed with an intrauterine fetal demise (IUFD) during her daily fetal heart rate check. Her laboratory work revealed hemolysis, worsening elevation of liver enzymes, thrombocytopenia, and acute kidney injury (AKI; ► **Table 1**). The patient delivered spontaneously without any intervention. Placental findings included diffuse perivillous fibrin deposition and maternal floor infarction.

Following delivery, the patient was transferred to the intensive care unit (ICU) with an oxygen saturation of 70% and required immediate intubation. Arterial blood sampling at this time resulted in a PaO₂:FiO₂ ratio of 164 consistent with adult respiratory distress syndrome (ARDS).⁸ Due to a low suspicion of preeclampsia with severe features or HELLP syndrome, the patient was not started on magnesium sulfate for seizure prophylaxis. The patient remained intubated with acute respiratory failure, ARDS, acute renal failure, and sepsis. Hemodialysis was started for anuria. She received ceftriaxone for 4 days for presumed bacterial superinfection, 5 days of azithromycin, 3 days of hydroxychloroquine, and two doses of tocilizumab. Computed tomography (CT) scan of the head showed an acute/subacute small- to moderate-sized right-middle cerebral artery vascular territory infarct and small left middle cerebral artery vascular territory infarct.

The second patient was a 31-year-old G2P1001 who presented to the emergency department at 29^{6/7} weeks of gestational age with decreased fetal movement. She reported a 1-week history of cough and fever to 102°F and like the first case sought medical attention on COVID-19 disease day 7. The physical exam was unremarkable. Urinalysis was noted to have +1 protein. Her blood pressure ranged from 115 to 133/77 to 89. Fetal heart rate monitoring was nonreassuring, and a biophysical profile for fetal assessment was 2/8 (two for a normal maximum vertical pocket). Emergent cesarean delivery was performed at which time, significant bleeding was noted. Platelets obtained during the cesarean section indicated 24,000/μL. Intraoperatively, the

Table 1 Summary of laboratory findings for cases 1 and 2

| Case | Baseline laboratories | PPD 0 | PPD 1 |
|-------------------|---|---|---|
| 41-year-old woman | COVID-19 day 7: complete blood count: 21.3 > 10.8/31.3 < 216 Blood urea nitrogen/creatinine: 9/0.51 Aspartate aminotransferase/alanine aminotransferase: 89/29 Lactate dehydrogenase: 296 C-reactive protein: 24 Prothrombin time/partial thromboplastin time: 12.6/36.7 < 1.19 D-Dimer: 0.54 | COVID-19 day 12: complete blood count: 25.3 > 12.7/87.4 < 48 Blood urea nitrogen/creatinine: 42/1.49 Aminotransferase/alanine aminotransferase: 192/88 Lactate dehydrogenase: 1,366 C-reactive protein: 8.4 Prothrombin time/partial thromboplastin time: 14.4/31.5 < 1.35 Fibrinogen: 185 D-Dimer: >35.2 Urinalysis: +1 protein | COVID-19 day 13: complete blood count: 51.3 > 10.6/32.8 < 41 Blood urea nitrogen/creatinine: 97/6.35 Aminotransferase/alanine aminotransferase: 172/204 Lactate dehydrogenase: 5,540 |
| 31-year-old woman | 1st prenatal visit (October 2019): Complete blood count: 6.8 > 13.5/40.2 < 212 | COVID-19 day 7: Complete blood count: 5.6 > 14.8/44.2 < 24 Peripheral smear: platelets decreased, slight schistocytes, bands Basic metabolic panel: 137/3.5/100/28/6/0.5 < 116 Aspartate aminotransferase/alanine aminotransferase: 43/17 Prothrombin time/partial thromboplastin time: 12/32.4 < 1 Fibrinogen: 97 Urinalysis: +1 protein | COVID-19 day 8: Complete blood count: 11.36 > 10.2/30.2 < 110 Fibrinogen: 181 Procalcitonin: 0.12 Lactate: 2.7 |

Abbreviations: COVID-19, novel coronavirus disease 2019; PPD, postpartum day.

patient was transfused two units of fresh frozen plasma (FFP) and two units of super-packed platelets. Postoperatively, a nasopharyngeal SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test was performed and was found to be positive, 7 hours following her emergent cesarean delivery. Pathological examination of the placenta included acute and chronic (predominantly chronic) villitis, intervillitis (predominantly chronic), and perivillous fibrin deposition likely representing severe placental hemorrhage consistent with disseminated intravascular coagulation (DIC). CT of the chest from postoperative day 1 revealed subtle peripheral opacities in the lower lobes.

Shortly after delivery, the neonate was intubated and transferred to the neonatal ICU (NICU). Initial laboratory findings revealed an elevated white blood cell count (28.06 cells/ μ L) and a normal platelet count (224,000/ μ L). Chest X-ray showed diffuse ground-glass appearance throughout both lung fields. On the second day of life, the neonate's white blood cell count normalized and CRP was found to be within normal limits. However, significant transaminitis was noted with aspartate aminotransferase/alanine aminotransferase of 362/321 U/L. Interestingly, the neonate's platelets down trended and reached a nadir of 66,000/ μ L on day 6 of life and ultimately, the fetus was confirmed to be positive for SARS-CoV-2.

The postoperative course for patient 2 was complicated by acute blood loss anemia (–Table 1) and she was transfused two units of packed red blood cells. The patient's platelets up trended postoperatively (–Table 1) and her COVID-19 symptoms remained mild. She never required medical treatment for COVID-19 symptoms or supplemental oxygen. The patient was discharged on postoperative day 4.

Discussion

HELLP complicates 0.5 to 1% of pregnancies and approximately 20% of HELLP occurs with severe preeclampsia.⁹ AKI is commonly associated with HELLP, complicating 7 to 15% of cases. HELLP is widely considered to be a severe form of preeclampsia, yet up to 15 to 20% patients do not have antecedent signs or symptoms of preeclampsia.¹⁰ The syndrome is progressive in nature. The pathophysiology of

HELLP is not entirely clear and there are several theories that try to isolate the trigger for this disease spectrum. The pathophysiological process of HELLP presents with endothelial damage resulting from platelet activation, leading to platelet aggregation. HELLP may also be associated with DIC, and in fact, some investigators believe that DIC is the primary process.⁹ Seventy percent of HELLP cases develop in the third trimester, while 30% develop within 48 hours of postpartum; delivery is considered first-line treatment. The additional use of magnesium sulfate for the prevention of progression to eclampsia is recommended, as well as the treatment of elevated blood pressure with antihypertensives.⁹

Much of the research on COVID-19 and its effects on pregnant patients and unborn fetuses is currently under investigation. Reports already exist of elevated liver enzymes, thrombocytopenia, DIC, cardiomyopathy, AKI, and ARDS in the general population.¹¹⁻¹⁴ Pregnant patients are likely to present with similar signs and symptoms, and many, if not all, of the same laboratory abnormalities as the general population.^{7,15,16} Research on the immediate and long-term maternal and fetal effects is still limited.

Although the similarities between COVID-19 and HELLP are evident (–Table 2), it is essential to focus on some of the clinical criteria that could help the obstetrician differentiate between the two. The first is the presence or absence of an elevated blood pressure. In up to 20% of HELLP cases, mild-to-severe range blood pressures will be evident, compared with patients with COVID-19, who have normal to low blood pressures, depending on the severity of the disease. The presence of a fever, leukocytosis, respiratory distress, and hypoxia will increase the suspicion of COVID-19. Proteinuria, in the context of AKI should be monitored and treated, but is unlikely to clarify the diagnosis. D-dimer has been used widely as an initial screening parameter for COVID-19, yet its sensitivity in pregnancy is known to be low.⁷ Although van der Pol et al have set a useful D-dimer parameter in pregnancy to help rule out pulmonary embolism using the pregnancy-adapted YEARS diagnostic algorithm,^{17,18} further studies are needed to determine its role in pregnancies affected by COVID-19. With that said, chest X-ray or CT is of benefit, since the presence of “ground

Table 2 Comparison of HELLP syndrome and COVID-19

| | HELLP syndrome | COVID-19 |
|-------------------------|---|---|
| Clinical manifestations | Nausea, vomiting, diarrhea, malaise, abdominal pain, midepigastic pain, headache, jaundice, visual changes, \pm elevated blood pressure | Diarrhea, malaise, headache, cough, fevers, tachypnea, hypoxia |
| Laboratory findings | Hemolysis, transaminitis, elevated LDH, elevated BUN/creatinine, thrombocytopenia, \pm proteinuria | Hemolysis, transaminitis, elevated LDH, elevated BUN/creatinine, thrombocytopenia, elevated D-dimer |
| Complications | DIC, liver infarction, renal failure, pulmonary edema | Cardiopulmonary arrest, ARDS, septic shock, renal failure, cardiomyopathy, DIC |
| Treatment | Delivery | Investigational. currently in our institution the regimen is: azithromycin, cephalosporins and hydroxychloroquine |

Abbreviations: ARDS, adult respiratory distress syndrome; BUN, blood urea nitrogen; COVID-19, novel coronavirus disease 2019; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; LDH, lactate dehydrogenase.

glass appearance,” or “patchy infiltrates” can help differentiate COVID-19 from pulmonary edema that could rarely be evident in patients with HELLP.^{19,20}

Furthermore, early chest imaging could be a useful tool to differentiate the diseases if laboratory abnormalities present later in disease progression. Early documentation of a respiratory infectious process could help avoid confusion once changes indicating HELLP occur. The final clue will likely present only after delivery. While HELLP will begin to resolve 24 to 72 hours of postpartum, the COVID-19 course is likely to be unrelated to the timing of delivery; yet more research is needed to clarify these outcomes.

Similarly, in centers where rapid viral testing is possible, our case series supports the practice of early testing of pregnant patients regardless of disease severity. Early documentation of a positive COVID-19 test could help the obstetrician be on high alert and foster collaboration with a multidisciplinary team, including intensivists, neonatologists, and maternal-fetal medicine specialists for close monitoring and possible need for intubation and early delivery. Anticipatory testing can also help in clarifying the etiology of clinical and laboratory changes indicating HELLP, if gradual progression occurs.

Conclusion

In conclusion, the differential diagnosis of HELLP should be considered in women with COVID-19 to avoid iatrogenic preterm delivery, delay in treatment, and complications of both undiagnosed and untreated HELLP and COVID-19.

Conflict of Interest

None.

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