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Third trimester placentitis: an underreported complication of SARS-CoV-2 infection

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SARS-CoV-2-related placentitis shows distinctive histologic characteristics, and its impact on perinatal outcomes is increasingly under scrutiny. We present two such cases in the third trimester displaying mild maternal clinical symptoms and associated with maternal coagulopathy, reduced fetal movements, and nonreassuring fetal heart rate tracing. Both cases resulted in emergency cesarean deliveries. Our cases and a review of the literature highlight that SARS-CoV-2 undermines placental function and thus greatly impacts late-term pregnancies, even in the absence of severe systemic disease.

Introduction

SARS-CoV-2 has posed many challenges in healthcare, including obstetrics. Recently, a particular complication of COVID-19 during the third trimester, suggestive of a placental-induced pathology, has been illustrated in a small number of case reports.1−9 Following the onset of the disease, parturients with mild symptoms developed reduced fetal movements, abnormal cardiotocography, and coagulopathy, warranting emergency delivery.

Between March 2020 and June 2021, 112 pregnant women tested positive for SARS-CoV-2 in our center. Two of these women (1.7%) had clinical presentation similar to that reported in previous publications. Our study aimed to present these 2 cases and review the available literature with regard to clinical presentation, maternal coagulation abnormalities, fetomaternal outcome, and placental pathology findings in such a distinctive manifestation of the disease.

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Cases

Case 1

A 33-year-old para 3, gravida 2 at 38+1 weeks of gestation, presented with decreased fetal movements. She reported cough and low-grade fever for the previous 7 days; the oxygen saturation rate was 97%. Her blood pressure was normal. A SARS-CoV-2 RNA polymerase chain reaction (PCR) test was positive 3 days previously. The fetal heart rate was nonreassuring, with a baseline rate of 170 beats per minute, a diminution in variability, and repeated decelerations. No proteinuria was noted on urinalysis. The platelet count was 18 × 10^9/L (normal range: 150 × 10^9/L–450 × 10^9/L), fibrinogen concentration was 1.2 g/L (normal range: 1.5–3.5 g/L), D-dimer was 69.3 mg/L (normal range: <0.5 mg/L), and activated partial thromboplastin time was 31.1 seconds (normal range: 21–35 seconds). A total of 3 g of fibrinogen, 4 units of platelets, and 3 units of fresh frozen plasma were administered before emergency cesarean delivery. A neonate weighing 3515 g (70th percentile) was delivered with Apgar scores of 1, 3, 5, and 8 at 1, 3, 5, and 10 minutes, respectively. No placenta abruption was found. The arterial umbilical blood gas pH was 7.18, and lactates were at 4.70 mmol/L. The neonate was admitted to the neonatal intensive care unit in isolation. Nasopharyngeal PCR tests were negative for SARS-CoV-2 at days 1 and 7 of life. Because the clinical course was uneventful, the neonate was discharged from hospital on day 8. The total maternal blood loss was 1000 mL. Following delivery, a progressive improvement in the patient coagulation screen was noted. The evolution was favorable, with the patient being discharged from hospital on day 8.

Pathologic examination of the placenta illustrated massive perivillous fibrin deposition, which involved more than 80% of the parenchyma. After a microscopic evaluation, the villi were observed to be surrounded by fibrin, filling almost the entire intervillous space. In addition, there was a chronic histiocytic intervillositis without associated villitis. We did not observe lesions suggestive of either maternal or fetal vascular malperfusion. The placental tissue was positive for SARS-CoV-2 on PCR testing, with a cycle threshold (CT) value of 23, indicating a very high viral load.
Case 2

A 33-year old gravida 2, para 1 at 36+2 weeks of gestation presented with reduced fetal movements, irregular contractions, and spotting. Seven days before that, she complained of general malaise and low-grade fever and tested positive for SARS-CoV-2. Her blood pressure, heart rate, and oxygen saturation were within normal limits. The protein-to-creatinine ratio was normal. Fetal heart rate monitoring was nonreassuring with a baseline of 160 beats per minute, a reduction in variability, and repeated decelerations. Her laboratory work showed thrombocytopenia (platelet count 94 x 10^9/L), low fibrinogen (1.9 g/L), and elevated D-dimer (20.4 mg/L). An emergency cesarean delivery was performed. A healthy male infant weighing 2515 g (25th percentile) was delivered, with an Apgar score of 7 and 8 at 5 and 10 minutes, respectively. There was no evidence of placental abruption. The newborn stayed with his mother in isolation and tested negative for SARS-CoV-2. There were no postoperative complications. The patient made a good recovery and was discharged with the newborn on postoperative day 5.

As in the previous case, perivillous fibrin deposition in 60% of the parenchyma associated with chronic histiocytic intervillositis without villitis was observed. SARS-CoV-2 PCR testing of the placenta returned a positive result with a CT value of 32, indicating a moderate viral load.

Discussion

We report 2 cases of mild SARS-CoV-2 maternal infection during the third trimester, who, 1 week after the onset of symptoms, developed reduced fetal movements, nonreassuring fetal heart rate tracings, and coagulation screen abnormalities, leading to prompt cesarean delivery. To date, 9 such cases have been published in literature.1−9 The findings are summarized in the Table.

The coexistence of similar placental abnormalities (chronic histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis) and moderate to high placental viral loads indicate that the infection was significant with regard to the patients’ presentations.1−9

SARS-CoV-2 infection of the syncytiotrophoblast has been suggested as a key contributor to these placental anomalies.10 Syncytiotrophoblast infection leads to complement activation, drawing monocytes to the site of injury by cytokine up-regulation.10 In turn, the inflammatory cytokines simultaneously cause a local procoagulant environment, resulting in the deposition of fibrin and thus placental dysfunction.

A recent prospective multicentric study of 165 unvaccinated COVID-19-positive pregnant women illustrated that SARS-CoV-2 placentitis was present only in a minority of patients (7.8%).11 Intrauterine fetal death was observed in half of these cases and was associated with extensive involvement of the placenta.11 In contrast, in liveborn placentas, only focal involvement of the placenta was seen (<25%).11 Varying time periods between the onset of maternal infection and fetal distress or intrauterine fetal demise have been reported from a couple of days to several weeks (with an

| Study | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Age (y) | 40 | 31 | 27 | 30 | 23 | 31 | 31 | 34 | 29 |
| Parity | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Maternal comorbidity | None reported | None reported | None reported | None reported | None reported | None reported | None reported | None reported | None reported |
| Onset (GA, wk) | 35+3 | 28+6 | 30+1 | 30+6 | 35+0 | 35+6 | 35+6 | 35+6 | 35+6 |
| Onset symptoms | Cough, fever | Cough, fever | Headache, malaise, coughing, shortness of breath, fever, reduced fetal movements | General malaise, myalgia, fever, myalgia, | Cough, fever | Cough, fever | Cough, fever | Cough, fever | Cough, fever |
| Clinical evolution | Thrombocytopenia | Transaminitis | Transaminitis | Transaminitis | Transaminitis | Transaminitis | Transaminitis | Transaminitis | Transaminitis |
| (continued) | | | | | | | | | |

Clinical Perspective
| Study | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 | Case 9 |
|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Viachodimitropoulou et al. (2020) | Futterman et al. (2020) | Mongula et al. (2020) | Schoenmakers et al. (2021) | Vivanti et al. (2020) | Linehan et al. (2021) | Kim et al. (2020) | Favre et al. (2021) | Favre et al. (2021) | |
| Laboratory value | | | | | | | | | |
| Hemoglobin (g/dL) | 12.3 | 5.6 | 6.2 | N/A | 12.0 | N/A | 14.8 | N/A | N/A |
| Platelets (10^9/L) | 82 | 24 | 104 | N/A | 54 | N/A | 24 | 63 | N/A |
| Fibrinogen (g/L) | 2.2 | 1.0 | 0.7 | N/A | 0.6 | N/A | N/A | N/A | N/A |
| D-dimer (mg/L) | 25.8 | 27 | N/A | >20 | N/A | N/A | N/A | 14.8 | N/A |
| aPTT (s) | 41 | 32.4 | 45 | N/A | 60 | N/A | N/A | N/A | N/A |
| Aspartate aminotransferase (unit/L) | 52 | 43 | 29 | N/A | 81 | N/A | N/A | N/A | N/A |
| Alanine aminotransferase (unit/L) | 20 | 17 | 9 | N/A | 41 | N/A | N/A | N/A | N/A |
| Delivery (GA, wk) | 35+5 | 29+7 | 32+1 | 31+4 | 35+5 | 37+3 | 29+6 | 29+1 | 32+1 |
| Issue | CD | CD | CD | CD | CD | CD | CD | CD | CD |
| Neonatal outcome | | | | | | | | | |
| Newborn weight (g) | 2430 | N/A | 1940 | 1880 | 2540 | 2800 | 1330 | 1370 | 1800 |
| Apgar score (1, 5, 10 mins) | 9/9 | N/A | 3/6/10 | 1/4/6 | 4/2/7 | 4/8 | 3/5/7 | 4/8/8 | 2/4/5 |
| Arterial blood gas | N/A | N/A | 7.28 | N/A | 7.27 | N/A | N/A | N/A | 6.69 |
| Neonatal intensive care unit | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| SARS-CoV-2 positive | Yes | Yes | N/A | No | Yes | N/A | No | Yes | No |
| Complications | None | Thrombopenia, transaminitis | None | Fetal inflammatory multisystem-like syndrome | Bilateral gliosis of the deep white periventricular and subcortical matter | None | None | Bilateral fronto parieto-occipital cystic periventricular leukomalacia | Parenchymal hemorrhagic sequelae Widespread cystic peri- ventricular leukomalacia |
| Maternal outcome | Postpartum hemorrhage Full recovery | Full recovery | Postpartum hemorrhage Full recovery | Full recovery | Full recovery | Full recovery | Full recovery | Full recovery | Full recovery |
| Placental pathology | | | | | | | | | |
| Perivillous fibrin deposition | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes |
| Chronic histiocytic interstitialis | Yes | Yes | Yes | Yes | Yes | Yes | N/A | Yes | Yes |
| SARS-CoV-2 positive | Yes | Yes | N/A | Yes | Yes | Yes | N/A | Yes | Yes |

Normal range: hemoglobin (12—17 g/dL); platelets (150 × 10^9 — 450 × 10^9/L), fibrinogen (1.5—3.5 g/L), D-dimer (<0.5 mg/L), aPTT (21—35 s), aspartate aminotransferase (9—40 unit/L); alanine aminotransferase (7—50 unit/L).
aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CD, cesarean delivery; GA, gestational age; N/A, not available; NRPFR, nonreassuring fetal heart rate.

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average of 1 week). Similar observations were drawn by other authors, suggesting a variability in pregnancy outcomes depending on the extension of lesions in the placenta parenchyma.

Most of the women presented with HELLP (hemolysis, elevated liver enzymes, low platelet count)-like syndrome features with varying degrees of coagulation screen disturbance. It is thought that SARS-CoV-2 infection causes dysregulation in the renin–angiotensin system (RAS). In vivo, the serum levels of preeclampsia markers such as soluble fms-like tyrosine kinase-1 and angiotensin II type 1-receptor autoantibodies were found to be higher in SARS-CoV-2 positive women with placent al infection than those who were uninfected. These local RAS alterations present potential mechanisms for the endothelial dysfunction and coagulopathy shown in our patients.

Obstetrical care in the context of COVID-19 infection was initially focused on the risk of respiratory failure in pregnant women and the possibility of vertical transmission. As the pandemic has progressed, we have come to understand that maternal infection has other important ramifications, notably placental injury with consequent severe fetal morbidity and mortality. SARS-CoV-2 placentitis may present only with reduced fetal movements following mild respiratory symptoms. In the absence of improved diagnostic criteria, clinicians treating COVID-19-positive patients with this presentation should apply a low threshold for fetal monitoring and coagulopathy screening even in the absence of severe systemic illness.

REFERENCES
1. Vlachodimitropoulou Kournoutsea E, Vivanti AJ, Shehata N, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost 2020;18:1648–52.
2. Futterman I, Toaff M, Navi L, Clare CA. COVID-19 and HELLP: overlapping clinical pictures in two gravid patients. AJR Rep 2020;10:e179–82.
3. Mongula JE, Frenken MWE, van Lijnschoten G, et al. COVID-19 during pregnancy: non-reassuring fetal heart rate, placental pathology and coagulopathy. Ultrasound Obstet Gynecol 2020;56:773–6.
4. Schoenmakers S, Snijder P, Verdijk RM, et al. Severe acute respiratory syndrome coronavirus 2 placent al infection and inflammation leading to fetal distress and neonatal multi-organ failure in an asymptomatic woman. J Pediatric Infect Dis Soc 2021;10:556–61.
5. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11:3572.
6. Linehan L, O’Donoghue K, Dineen S, White J, Higgins JR, Fitzgerald B. SARS-CoV-2 placentitis: an uncommon complication of maternal COVID-19. Placenta 2021;104:261–6.
7. Kim JH, Shrestha N, Girshin M. Unexpected severe thrombocytopenia in the COVID-19 positive parturient. Anesth Analg 2020;131:e116–7.
8. Favre G, Mazzetti S, Gengler C, et al. Decreased fetal movements: a sign of placental SARS-CoV-2 infection with perinatal brain injury. Viruses 2021;13:2517.
9. Kirtsman M, Diambomba Y, Poutanen SM, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ 2020;192:E647–50.
10. Watkins JC, Torous VF, Roberts DJ. Defining severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) placentitis: a report of 7 cases with confirmatory in situ hybridization, distinct histomorphologic features, and evidence of complement deposition. Arch Pathol Lab Med 2021;145:1341–9.
11. Konstantinidou AE, Angelidou S, Havaki S, et al. Stillbirth due to SARS-CoV-2 placentitis without evidence of intrauterine transmission to fetus: association with maternal risk factors. Ultrasound Obstet Gynecol 2022;59:813–22.
12. Dubucs C, Groussettes M, Ousselin J, et al. Severe placental lesions due to maternal SARS-CoV-2 infection associated to intrauterine fetal death. Hum Pathol 2020;52:46–55.
13. Verma S, Joshi CS, Silvstein RB, He M, Carter EB, Mysorekar IU. SARS-CoV-2 colonization of maternal and fetal cells of the human placenta promotes alteration of local renin-angiotensin system. Med (NY) 2021;2:575–90, e5.