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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.

Cite this article as: Sichitiu J, Bourgon N, Guilleminot T, et al. Third trimester placentitis: an underreported complication of SARS-CoV-2 infection. Am J Obstet Gynecol MFM 2022;4:100703.

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Received April 6, 2022; revised July 13, 2022; accepted July 28, 2022.

The authors report no conflict of interest.

No funding was obtained for this work.

A consent form was signed by both patients.

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2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2022.100703

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 94×10^9/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

TABLE
Third trimester placentitis: data from published articles

Study	Case 1 Vlachodimitropoulou et al,[1] (2020)	Case 2 Futterman et al,[2] (2020)	Case 3 Mongula et al,[3] (2020)	Case 4 Schoenmakers et al,[4] (2021)	Case 5 Vivanti et al,[5] (2020)	Case 6 Linehan et al,[6] (2021)	Case 7 Kim et al,[7] (2020)	Case 8 Favre et al,[8] (2021)	Case 9 Favre et al,[8] (2021)
Age (y)	40	31	27	30	23	26	31	34	29
Parity	0	1	1	0	0	0	1	0	0
Maternal comorbidity	Familial neutropenia, gestational diabetes mellitus	None reported	Type 1 diabetes	Obesity	None reported	Hypothyroidism	None reported	None reported	Gestational diabetes mellitus
Onset (GA, wk)	35+3	28+6	30+1	30+6	35+0	36+5	28+6	28+4	31+0
Onset symptoms	Cough, fever	Cough, fever	Headache, malaise, coughing, shortness of breath, fever, reduced fetal movements	General malaise, myalgia, fever	Cough, fever	Fever, cough, rigors, abdominal pain, headache, reduced fetal movements	Cough, fever	Chills, fever, myalgia, ageusia, and anosmia	Fever, flu-like symptoms
Clinical evolution	Thrombocytopenia Fibrinogen decline Prolonged aPTT Transaminitis	NRFHR Reduced fetal movement Thrombocytopenia Fibrinogen decline Prolonged aPTT Transaminitis	NRFHR Thrombocytopenia Anemia Fibrinogen decline	NRFHR Reduced fetal movements	NRFHR Thrombocytopenia Fibrinogen decline Prolonged aPTT Transaminitis	NRFHR Persistence of reduced fetal movements	NRFHR Reduced fetal movements Thrombocytopenia	NRFHR Reduced fetal movements Thrombocytopenia	NRFHR Reduced fetal movements

(continued)

TABLE

Third trimester placentitis: data from published articles *(continued)*

Study	Case 1 Vlachodimitropoulou et al,[1] (2020)	Case 2 Futterman et al,[2] (2020)	Case 3 Mongula et al,[3] (2020)	Case 4 Schoenmakers et al,[4] (2021)	Case 5 Vivanti et al,[5] (2020)	Case 6 Linehan et al,[6] (2021)	Case 7 Kim et al,[7] (2020)	Case 8 Favre et al,[8] (2021)	Case 9 Favre et al,[8] (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	N/A	27	N/A	>20	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 intervillitis	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes
SARS-CoV-2 positive	Yes	N/A	Yes	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 amniotransferase; ALT, alanine amniotransferase; *CD*, cesarean delivery; *GA*, gestational age; *N/A*, not available; *NRFHR*, nonreassuring fetal heart rate.

Sichitiu. SARS-CoV-2 infection and third trimester placentitis. Am J Obstet Gynecol MFM 2022.

average of 1 week).[11] Similar observations were drawn by other authors, suggesting a variability in pregnancy outcomes depending on the extension of lesions in the placenta parenchyma.[12]

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).[13] 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 placental infection than those who were uninfected.[13] These local RAS alterations present potential mechanisms for the endothelial dysfunction and coagulopathy shown in our patients.[13]

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. ■

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