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Case Report

Placental Infection with Different SARS-CoV-2 Variants Leading to Stillbirth: Report of Two Cases

Miriam A. Snow [1], Medini K. Annavajhala [2], Sofia Z. Moscovitz [3], Anne-Catrin Uhlemann [3] and Larisa Debelenko [1,*]

[1] Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY 10032, USA; mah2228@cumc.columbia.edu
[2] Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA; annavajham@chop.edu
[3] Department of Medicine, Division of Infectious Diseases, Columbia University Irving Medical Center, New York, NY 10032, USA; szm2110@cumc.columbia.edu (S.Z.M.); au2110@cumc.columbia.edu (A.-C.U.)
* Correspondence: ld2863@cumc.columbia.edu

Abstract: SARS-CoV-2 placental infection, also known as placentitis (SP), is an established cause of stillbirth; however, this pathology is rare and its incidence across different viral variants is unknown. We report two new cases of SP-associated stillbirth in the third trimester of pregnancy. The cases were identified by a retrospective review of 84 fetal autopsies performed at our institution from 1 March 2020 to 1 March 2024. In one case, the mother was previously healthy and asymptomatic for COVID-19. In the second case, the mother had a history of multiple sclerosis (MS) and suffered recurrent moderate-to-severe COVID-19. In both cases, the placentas showed SP with massive perivillous fibrin deposition (PVFD), involving more than 90% of placental discs, resulting in placental insufficiency and lethal hypoxic–ischemic injury to the fetuses. Placental tissues were positive for SARS-CoV-2 by in situ hybridization (ISH) and immunohistochemistry (IHC). Sequencing revealed the delta variant in Case 1 and omicron XBB.1.515 in Case 2. The data demonstrate that SP, albeit rare, continues to cause intrauterine fetal demise (IUFD) across viral variants regardless of the clinical severity of the infection. The persistence of rare cases of SP as COVID-19 becomes globally endemic emphasizes the importance of disease prevention in pregnancy.

Keywords: SARS-CoV-2; placenta; fetus; stillbirth

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1. Introduction

COVID-19 has been associated with adverse effects on women's health in pregnancy and childbirth, including higher rates of maternal mortality, hospitalization, admission to the intensive care unit, mechanical ventilation, preterm birth, gestational hypertension and stillbirth [1–3]. In the first pandemic year, statistical data indicated only a slight increase in the rates of stillbirth as compared to pre-pandemic rates; however, a significant increase was detected during the delta variant prevalence in late 2021. Thus, 0.98% of COVID-19-affected deliveries pre-delta and 2.70% during the delta period resulted in stillbirth [4]. The association between stillbirth and newly emerging virulent SARS-CoV-2 strains is controversial. Although some studies indicated little or no effect of infection on pregnancy outcomes during the omicron circulation [5,6], several other reports demonstrated pregnancy risks with omicron similar to those associated with the alpha and delta variants [7,8].

The pathologic process directly responsible for stillbirth in SARS-CoV-2 infection has been known as SARS-CoV-2 placentitis (SP), defined as a histopathological triad with concomitant

detection of SARS-CoV-2 in placental tissue [9]. The placenta responds to SARS-CoV-2 by (1) inflammation localized to the intervillous compartment (intervillositis); (2) necrosis of villous trophoblasts, a significant part of which is due to direct viral cytopathic effects on this cell type; and (3) rapidly progressive and massive perivillous fibrin deposition (PVFD), which obliterates the feto-maternal interface (placental barrier). This leads to placental insufficiency and subsequent intrauterine fetal demise (IUFD) from severe fetal hypoxia in cases when the process progresses to involve more than 75% of the placental disc [10].

SP is rare and, although the exact incidence is unknown, it has been reported in 1.5–12% of infected parturient women whose placentas have been examined by pathology [6,11–14]. SP is a serious manifestation of SARS-CoV-2 infection and is associated with stillbirth in up to 50% of documented cases [6,15–19]. The mechanism underlying the development of SP in a small percentage of infected pregnant women remains unclear, but it is likely related to SARS-CoV-2 viremia, which is also rare in pregnancy [20]. The disease shows no correlation with the clinical severity of maternal COVID-19 and is frequently asymptomatic, although thrombocytopenia and decreased fetal movements have been reported in approximately 50% of cases [6,12,21,22].

Herein, we analyze all cases of fetal demise which underwent autopsy with placental examination at our institution during 4 years of the COVID-19 pandemic and identified two cases of fatal SP. These were associated with different viral strains, which were prevalent in the corresponding months.

2. Materials and Methods

This study was approved by the institutional review board. We performed a retrospective analysis of fetopsies from the pathology files of our institution during 4 years of the COVID-19 epidemic (from 1 March 2020 to 1 March 2024). Clinical information was extracted from electronic medical records. A total of 84 fetal autopsies with concomitant placental examinations were performed during this period. In 2 cases, maternal SARS-CoV-2 nasopharyngeal PCR tests were positive at the time of delivery. Pathology reports and slides were re-reviewed by 2 pathologists (MS, LD). Placental and fetal tissues were studied by SARS-CoV-2 in situ hybridization (ISH) and immunohistochemistry (IHC) using techniques and reagents described **previously [23]**. RNA from tissue samples was extracted using Quick-RNA FFPE Miniprep with the optional xylene deparaffinization protocol (Zymo Research, Irvin, CA, USA). An xGen SARS-CoV-2 Amplicon Panel (Integrated DNA technologies, Coralville, IA, USA) was used to perform tiled amplification of the viral genome, utilizing the low input protocol recommendations. Amplicons were barcoded using an Oxford Nanopore Native Barcoding Expansion 96 kit (NBD114.96) (Oxford Nanopore Technologies, Oxford, UK) and sequenced on an Oxford Nanopore GridION R10.4.1 flow cell. Sequencing reads were mapped to the NC_045512.2 reference genome using *minimap2* (https://lh3.github.io/minimap2/ (accessed on 6 December 2024)) and lineages in each sample were identified using *freyja* (https://github.com/andersen-lab/Freyja (accessed on 6 December 2024)).

3. Detailed Case Description

3.1. Case 1

A 30-year-old pregnant woman, gravida 3 para 0, presented to the emergency room with acute abdominal pain for 2 days at 31 4/7 weeks of gestation. The patient had no significant antenatal medical history and the pregnancy course was largely uncomplicated. She reported abdominal tightening and excessive fetal movements but denied vaginal bleeding or leakage of fluid. The patient denied any headache, congestion, vision, smell or hearing changes, sore throat, difficulty swallowing, neck stiffness, chest pain, palpitations, coughing and shortness of breath, nausea, vomiting, diarrhea, urinary symptoms, extremity

swelling, or muscle or joint pains. The physical exam was unremarkable. Her compete blood count, including platelets, was within normal range. IUFD was diagnosed by ultrasound and shortly afterwards she spontaneously delivered a stillborn female fetus and placenta. A SARS-CoV-2 nasopharyngeal PCR test was positive on admission to labour and delivery. Vaccination records were not available.

The fetopsy showed a macerated female fetus in the 25–50th percentile for weight, with periorbital edema and small pleural and peritoneal effusions consistent with mild fetal hydrops. No dysmorphic features or congenital anomalies were identified. Microscopic examination revealed signs of meconium aspiration indicative of a fetal hypoxic–ischemic injury and was otherwise unremarkable. A fetal nasopharyngeal swab SARS-CoV-2 PCR test was positive; however, SARS-CoV-2 IHC was negative in the neck, lung and heart tissues.

The accompanying placenta was in the 10th percentile for weight. Gross examination was remarkable for subchorionic and scattered intraparenchymal hematomas that involved approximately 20% of the placental disc. The remaining parenchyma was diffusely pale, firm and somewhat gritty (Figure 1A). Microscopic examination revealed acute and chronic intervillositis with trophoblast necrosis and massive perivillous fibrin deposition involving more than 90% of intervillous space (Figure 1B). SARS-CoV-2 IHC detected viral proteins in villous trophoblasts, stroma and fetal endothelium (Figure 1C). ISH using a double-stranded SARS-CoV-2 probe was positive in villous trophoblasts, indicating viral replication in this cell population. The cause of death was severe hypoxic–ischemic injury with fetal hydrops due to placental insufficiency caused by SP with massive PVFD and transplacental SARS-CoV-2 infection.

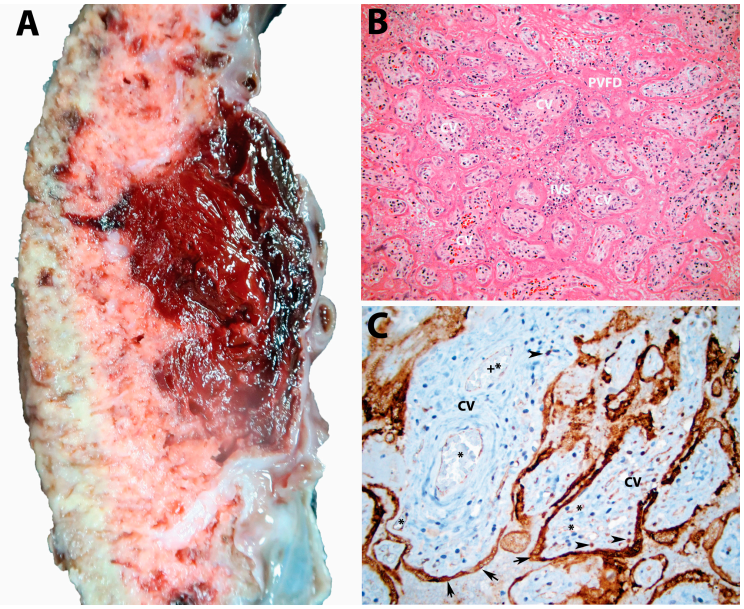

Figure 1. Gross and microscopic placental pathology, Case 1. (**A**) Slice of placental tissue with diffuse parenchymal consolidation and subchorionic hematoma; (**B**) microscopy of the placenta with chorionic villi (CV) encased in fibrillary material occupying maternal perivillous space, the so-called massive perivillous fibrin deposition (PVFD), with areas of mixed inflammatory infiltrates (intervillositis, IVS). Hematoxylin–eosin stain, x200; (**C**) immunohistochemical detection of SARS-CoV-2 nucleocapsid protein with signal (brown chromogen) in trophoblastic lining (arrows) of chorionic villi (CV), endothelium of fetal capillaries (asterisk), and villous stromal cells (arrowheads). Anti-SARS-CoV-2 nucleocapsid rabbit monoclonal antibody, clone 0001 (mAb 001); dilution 1:5000 (Sino Biological, Wayne, PA, USA), x400.

Sequencing analysis of placental homogenates, performed later as a part of this study, detected the delta SARS-CoV-2 variant (AY.X), prevalent in the population at the time of

delivery (December of 2021); the exact sub-lineage could not be obtained due to low, partial sequencing coverage (65% genomic coverage with a mean depth of 6x).

3.2. Case 2

A 39-year-old gravida 1 para 0 pregnant woman with multiple sclerosis (MS) treated with rituximab conceived by in vitro fertilization. She reported a single dose of the Pfizer COVID-19 vaccine in April 2021 and COVID-19 infection in November 2021, 8 months prior to conceiving. At 26 weeks of pregnancy, she was diagnosed with a second SARS-CoV-2 infection presenting with mild sinusitis. One month later, after initial resolution of the infection, she was hospitalized with COVID-19 re-activation presenting with shortness of breath requiring treatment with supplemental oxygen, steroids and remdesivir. She also received treatment for influenza and bacterial coverage. One week following treatment for COVID-19 re-activation, she presented with contractions and absent fetal cardiac activity and spontaneously delivered a stillborn female fetus at 34 4/7 weeks. Her nasopharyngeal SARS-CoV-2 PCR test was still positive at the time of delivery. Her complete blood count was remarkable for mild leukocytosis, as well as mild anemia and thrombocytopenia. The coagulation panel was within normal range.

The fetopsy revealed a female fetus weighing 1910 g (in the 25th percentile for gestational age) with features of fetal hydrops (pericardial, pleural and peritoneal effusions) and signs of fetal hypoxia and stress, including acrocyanosis and meconium aspiration. No congenital anomalies or dysmorphic features were present. A fetal nasopharyngeal swab for SARS-CoV-2 was not performed; IHC for SARS-CoV-2 was negative in fetal lung tissue.

Placental examination showed a small-for-gestational-age placenta with scattered hemorrhages encompassing approximately 15% of placental parenchyma, which was otherwise diffusely consolidated (Figure 2A).

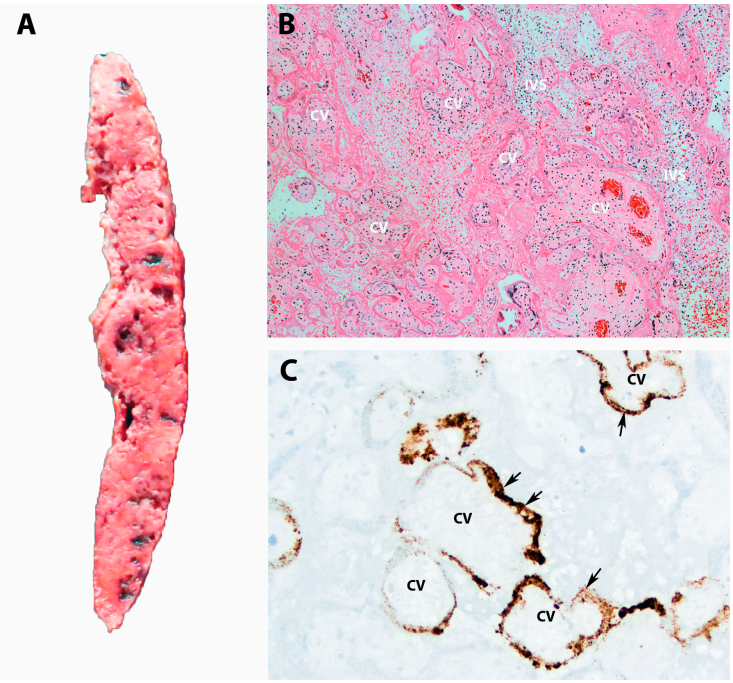

Figure 2. Gross and microscopic placental pathology, Case 2. (**A**) Slice of placental tissue with diffuse parenchymal consolidation and scattered small hemorrhages; (**B**) microscopy of the placenta with chorionic villi (CV) encased in perivillous fibrin with extensive areas of intervillous inflammation (IVS). Hematoxylin–eosin stain, x200; (**C**) in situ hybridization with double-stranded RNA probe showing SARS-CoV-2 signal (brown chromogen) in trophoblastic lining (arrows) of chorionic villi (CV). RNAscope-ProbeV-nCoV2019-S (Advanced-Cell-Diagnostics, Hayward, CA, USA); x400.

Microscopically, the features of SP were observed and included intervillositis, trophoblast necrosis and massive PVFD, involving more than 95% of the placental disc (Figure 2B). IHC against SARS-CoV-2 nucleocapsid protein was strongly positive in villous trophoblasts and maternal mononuclear cells localized in the intervillous space. ISH was consistent with viral replication in villous trophoblasts (Figure 2C). The cause of death was fetal hypoxic–ischemic injury attributed to placental insufficiency due to SP with massive PVFD.

Sequencing of the placental sample demonstrated the omicron XBB.1.5 variant of SARS-CoV-2 (92% genomic coverage with a mean depth of 57x), which was prevalent in the population at that time (February of 2023).

Case summaries are presented in Table 1.

Table 1. Clinical characteristics of 2 stillbirths due to SARS-CoV-2 placentitis.

Maternal Characteristics	Case 1	Case 2
Age, Gravity, Parity	30 yo G3P0020	39 yo G1P0
Maternal Medical History	Unremarkable	MS treated with rituximab
Antenatal History	First trimester bleeding, resolved	In vitro fertilization
SARS-CoV-2 PCR Status	Positive on admission for IUFD	Positive for 8 weeks prior to IUFD
Severity of COVID-19	Asymptomatic	Moderate-to-severe
Vaccination/Immunity Status	Unknown	One dose of Pfizer vaccine, early 2021 History of prior COVID-19, late 2021
Placental Characteristics		
Weight	261 g (small for gestational age)	292 g (small for gestational age)
Extend of SP with PVFD	More than 90%	More than 95%
Additional Placental Pathology	Subchorionic and intervillous hematomas Obliterative vasculopathy of stem vessels	Multiple intervillous hematomas
SARS-CoV-1 ISH	Positive in villous trophoblasts	Positive in villous trophoblasts
SARS-CoV-2 IHC	Positive in maternal macrophages, villous trophoblasts, villous stromal cells and endothelium of fetal capillaries	Positive in maternal macrophages, villous trophoblasts, villous stromal cells and endothelium of fetal capillaries
SARS-CoV-2 Sequencing	Delta variant	Omicron XBB.1.515 variant
Fetal Characteristics		
Date of Stillbirth	December 2021	February 2023
Gestational Age	31 weeks and 4 days	34 weeks and 4 days
Weight	1430 g (appropriate for gestational age)	1910 g (appropriate for gestational age)
Autopsy Findings	Fetal hydrops. Diffuse alveolar hemorrhage and meconium aspiration	Fetal hydrops Meconium aspiration
Nasopharyngeal SARS-CoV-2 PCR Test	Positive	Not performed
SARS-CoV-2 ISH and IHC in Fetal Organs	Negative	Negative

4. Discussion

Placental and fetopsy findings from the two cases of IUFD in women infected with SARS-CoV-2 were virtually identical: both featured SP involving more than 90% of placental discs resulting in placental insufficiency. Severe fetal hypoxic–ischemic injury with non-immune hydrops ensued, following the sequelae of fatal intrauterine SARS-CoV-2 infection reported previously [10]. Similarly to prior reports [10–12,21], no evidence of replicating virus was found in the fetal tissues.

The observed SARS-CoV-2 gross placental characteristics (diffusely firm, gritty consistency with scattered hemorrhages) were distinctive. This morphology should raise a suspicion of SP, prompting further microscopic and appropriate IHC studies. This becomes relevant since the universal SARS-CoV-2 PCR screening of pregnant and parturient women has been discontinued by many hospitals and the diagnosis of SP, which frequently develops in asymptomatic patients, can be missed if placentas are not studied with microscopy and IHC.

Our cases align with the published SP literature on the lack of correlation between placental involvement by SARS-CoV-2 infection and maternal COVID-19 disease severity [9–13] and further demonstrate that SP equally affects healthy women with asymptomatic or mild COVID-19 and women with moderate-to-severe COVID-19. In one of our cases, the women suffered from MS. Interestingly, another case of fatal SP in the setting of MS was reported in a series of cases from Greece [12]. Studies of COVID-19 in MS patients yielded controversial data on the severity of the infection in this patient population [24]; however, the second reported case of fatal SP in MS warrants further attention.

We detected the delta variant in the placenta of a patient with asymptomatic COVID-19; this finding is in keeping with the reported higher risks of stillbirth associated with this variant [4]. Identification of the omicron variant in the second case demonstrates the ability of this variant to cause fatal SP as well. Although generally known to be associated with milder disease, omicron XBB.1.5 was responsible for recurrent, prolonged moderate-to-severe COVID-19 in our second case, involving the MS patient previously treated with rituximab, which suppresses B-cell-mediated immunity. It has been proposed that aberrant immune responses play a role in the pathogenesis of idiopathic intervillositis with massive PVFD and may contribute to the same disease process caused by SARS-CoV-2 [25]. Thus, synergetic effects of omicron and compromised immunity cannot be ruled out in our second case of fatal SP.

The incidence of fatal SP cannot be concluded from our study. However, we can approximate that in our practice it is comparable to CMV and parvovirus B-19 infections, each of which was diagnosed as a cause of stillbirth once during the analyzed 4-year period. The incidence of ascending bacterial intrauterine infection leading to stillbirth in our practice was six times higher (12 cases during the analyzed period).

Although the COVID-19 pandemic was declared over as of May 2023, the infection remains globally endemic and the risks of pregnancy loss attributable to SARS-CoV-2, albeit low, persist. It is important that SP becomes a recognized disease entity by clinicians and pathologists alike, especially because SP can cause rapidly progressive fetal decline despite lack of maternal symptoms in half of the cases, making it difficult to detect and manage in a timely manner. In this clinical scenario, infection prevention is crucial. Although SARS-CoV-2 vaccination has proven safe in pregnancy, its utility remains uncertain in patients with immunosuppression or autoimmune disease who can show compromised vaccine responses [26]. Further studies are needed to optimize SARS-CoV-2 prevention strategies, detection and treatment options in pregnancy.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Columbia University in the City of New York (IRB-AAAT0272 approved on 6 June 2021).

Informed Consent Statement: Patient consent was waived due the following reasons: the research involved no more than minimal risk to the subjects; the waiver or alteration would not adversely affect the rights and welfare of the subjects; the research could not practicably be carried out without the waiver or alterations. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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