Placental Tissue Destruction and Insufficiency From COVID-19 Causes Stillbirth and Neonatal Death From Hypoxic-Ischemic Injury

A Study of 68 Cases With SARS-CoV-2 Placentitis From 12 Countries

David A. Schwartz, MD, MS Hyg; Elyzabeth Avvad-Portari, MD, PhD; Pavel Babáľ, MD, PhD; Marcella Baldewijns, MD, PhD; Marie Blomberg, MD, PhD; Amine Bouachba, MD; Jessica Camacho, MD; Sophie Collardeau-Frachon, MD, PhD; Arthur Colson, MD; Isabelle Dehaene, MD; Joan Carles Ferreres, MD, PhD; Brendan Fitzgerald, MB, BCh, FRC Path; Marta Garrido-Pontnou, MD; Hazem Gergis, MB, BCh, MSc, MRCOG (UK); Beata Hargitai, MD; A. Cecilia Helguera-Repetto, PhD; Sandra Holmström, MD; Claudine Liliane Irles, PhD; Åsa Leijonhfvud, MD; Sasha Libbrecht, MD; Tamás Marton, MD; Noel McEntagart, MB BCh BAO, FRC Path; James T. Molina, MD, PhD; Raffaella Morotti, MD; Alfons Nadal, MD, PhD; Alexandra Navarro, MD; Maria Nelander, MD, PhD; Angelica Oviedo, MD; Andre Ricardo Oyamada Otani, MD; Nikos Papadogiannakis, MD; Astrid C. Petersen, MD; Drucilla J. Roberts, MD; Ali G. Saad, MD; Anna Sand, MD, PhD; Sam Schoenmakers, MD, PhD; Jennifer K. Sehn, MD; Preston R. Simpson, MD; Kristen Thomas, MD; M. Yolotzin Valdespino-Vázquez, MD; Lotte E. van der Meeren, MD, PhD; Jo Van Dorpe, MD, PhD; Robert M. Verdijk, MD, PhD; Jaclyn C. Watkins, MD, MS; Mehreen Zaigham, MD

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From the Department of Pathology, Fernandes Figueira Institute, FIOCRUZ, Rio de Janeiro, Brazil (Avvad-Portari); the Department of Pathology, Faculty of Medicine, Comenius University, Bratislava, Slovakia (Babál); the Department of Pathology, University Hospitals Leuven, Leuven, Belgium (Baldewijns); the Department of Obstetrics and Gynecology and the Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden (Blomberg); the Institut de Pathologie Multisite des Hospices Civils de Lyon, Lyon, France (Bouachba); SOFFOET–Société Française de Fœtopathologie, Paris, France (Bouachba, Collardeau-Frachon); the Pathology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain (Camacho, Garrido-Pontnou, Navarro); the Department of Pathology, Hopital Femme-Mère Enfant, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Bron, France (Collardeau-Frachon); the Department of Obstetrics, Institute of Experimental and Clinical Research (IREC), Université Catholique de Louvain, Brussels, Belgium (Colson); the Departments of Obstetrics and Gynaecology (Dehaene) and Pathology (Van Dorpe), Ghent University Hospital, Ghent, Belgium; the Pathology Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Barcelona, Spain (Ferreres); the Department of Morphological Sciences, School of Medicine, Universitat Autònoma de Barcelona, Sabadell, Spain (Ferreres); the Department of Pathology, Cork University Hospital, Wilton, Cork, Republic of Ireland (Fitzgerald); the Department of Morphological Sciences, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain (Garrido-Pontnou); the Department of Obstetrics and Gynaecology, Doncaster and Bassetlaw NHS Teaching Hospitals, Women's Hospital, Doncaster, United Kingdom (Gergis); the Division of Perinatal Pathology, Department of Cellular Pathology, Birmingham Women's and Children's Hospital, NHS Foundation Trust, Birmingham, United Kingdom (Hargitai); the Departments of Immunobiochemistry (Helguera-Repetto) and Anatomical Pathology (Valdespino-Vázquez), National Institute of Perinatology, Mexico City, Mexico; the Department of Obstetrics and Gynaecology, Halland Hospital, Varberg, Sweden (Holmström); the Department of Physiology and Cellular Development, National Institute of Perinatology "Isidro Espinosa de los Reyes," Mexico City, Mexico (Irles); the Department of Obstetrics and Gynaecology, Helsingborg Hospital, Department of Clinical Science Helsingborg, Lund University, Lund, Sweden (Leijonhfvud); the Department of Pathological Anatomy, Antwerp University Hospital, Edegem, Belgium (Libbrecht); the Cellular Pathology Department, Birmingham Women's Hospital, Birmingham, United Kingdom (Marton); Histopathology, Rotunda Hospital, Dublin, Republic of Ireland (McEntagart); Pathology and Laboratory Medicine (Molina) and the Department of Pathology (Simpson), CHRISTUS Hospital St Elizabeth, Beaumont, Texas; the Department of Pathology and Pediatrics, Autopsy Service, Yale University School of Medicine, New Haven, Connecticut (Morotti); the Pathology Department, Hospital Clínic, Barcelona, Spain (Nadal); the Department of Basic Clinical Practice, School of Medicine, Universitat de Barcelona, and August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain (Nadal); the Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden (Nelander); Department of Pathology and Laboratory Medicine, Burrell College of Osteopathic Medicine, Las Cruces, New Mexico (Oviedo); Laboratório Ferdinando Costa, São Paulo, Brazil (Otani); the Department of Laboratory Medicine, Division of Pathology (Papadogiannakis) and the Department of Women's and Children's Health (Sand), Karolinska Institute, Stockholm, Sweden; the Departments of Pathology (Papadogiannakis), Karolinska University Hospital, Stockholm, Sweden; the Department of Pathology, Aalborg University Hospital, Aalborg, Denmark (Petersen); the Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (Roberts, Watkins); Pediatric Pathology and Neuropathology, Department of Pathology, University of Miami Miller School of Medicine/Jackson Health System/Holtz Children's Hospital, Miami, Florida (Saad); the Department of Obstetrics and Gynaecology, Karolinska University Hospital, Solna, Stockholm, Sweden (Sand); the Department of Obstetrics and Gynaecology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands (Schoenmakers, Verdijk); the Department of Pathology, St Louis University School of Medicine, St Louis, Missouri (Sehn); the Department of Pathology, NYU Langone Health–Main Campus & Bellevue Hospital Center, New York University School of Medicine, New York, New York (Thomas); the Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands (van der Meeren); the Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands (van der Meeren); Obstetrics & Gynecology, Institution of Clinical Sciences Lund, Lund University, Lund, Sweden (Zaigham); and the Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö and Lund, Sweden (Zaigham). Schwartz is in consultative practice of Perinatal Pathology, Atlanta, Georgia.

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Corresponding author: David A. Schwartz, MD, MS Hyg, 1950 Grace Arbor Ct, Atlanta, GA 30329 (email: davidalanschwartz@gmail.com).

• *Context.*—**Perinatal death is an increasingly important problem as the coronavirus disease 2019 (COVID-19) pandemic continues, but the mechanism of death has been unclear.**

Objective.—**To evaluate the role of the placenta in causing stillbirth and neonatal death following maternal infection with COVID-19 and confirmed placental positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).**

Design.—**Case-based retrospective clinicopathologic analysis by a multinational group of 44 perinatal specialists from 12 countries of placental and autopsy pathology findings from 64 stillborns and 4 neonatal deaths having placentas testing positive for SARS-CoV-2 following delivery to mothers with COVID-19.**

Results.—**Of the 3 findings constituting SARS-CoV-2 placentitis, all 68 placentas had increased fibrin deposition and villous trophoblast necrosis and 66 had chronic histiocytic intervillositis. Sixty-three placentas had massive perivillous fibrin deposition. Severe destructive placental disease from SARS-CoV-2 placentitis averaged 77.7% tissue involvement. Other findings included multiple intervillous thrombi (37%; 25 of 68) and chronic villitis (32%; 22 of 68). The majority (19; 63%) of the 30 autopsies revealed no significant fetal abnormalities except for intrauterine hypoxia and asphyxia. Among all 68 cases, SARS-CoV-2 was detected from a body specimen in 16 of 28 cases tested, most frequently from nasopharyngeal swabs. Four autopsied stillborns had SARS-CoV-2 identified in internal organs.**

Conclusions.—**The pathology abnormalities composing SARS-CoV-2 placentitis cause widespread and severe placental destruction resulting in placental malperfusion and insufficiency. In these cases, intrauterine and perinatal death likely results directly from placental insufficiency and fetal hypoxic-ischemic injury. There was no evidence that SARS-CoV-2 involvement of the fetus had a role in causing these deaths.**

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The emergence of new viral diseases has always created anxiety among persons at risk for infection, but perhaps this is most true for pregnant women, who fear not only for themselves but also for their unborn children. An important aspect of the current coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is its effect on pregnant women, the fetus, and the newborn. Previous experiences with the pathogenic coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), as well as other RNA respiratory viruses, had indicated that transplacental infections were either absent or rare.[1,2] Studies performed at the beginning phase of the current pandemic found that although pregnant women in China could develop infection with the newly identified coronavirus, the large majority of infected mothers had either mild or nonexistent symptoms and did not become more ill than did nonpregnant women of the same age, and that, except for a reported increase in premature delivery, there was little or no excess perinatal mortality.[3–6] As the virus spread throughout the world, the genome of SARS-CoV-2 developed mutations resulting in new genetic strains, with the most worrisome labeled as variants of concern. These included the alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2) strain variants.[7,8] Eventually, COVID-19 was found to be associated with adverse pregnancy outcomes including severe maternal illness as well as neonatal complications.[9,10] However, until recently, studies from multiple countries[11–16] failed to demonstrate any statistically significant association between COVID-19 in pregnant women and the occurrence of stillbirth. With the increasing spread of these new viral strains during successive waves of infection, anecdotal experiences by pathologists and clinicians together with some published reports suggested that increasing numbers of pregnant women infected with SARS-CoV-2 were having stillbirths.[17–20] This was supported in April 2021 when a cluster of 6 stillborn fetuses and 1 miscarriage occurred in mothers with COVID-19 from Ireland,[17–21] and then in May 2021 when a population-based cohort study from England demonstrated an increased risk among pregnant women infected with SARS-CoV-2 for having a fetal death.[22] The association of SARS-CoV-2 infection and stillbirth was confirmed on November 26, 2021, when the US Centers for Disease Control and Prevention reported a population-based study showing that pregnant women with COVID-19 had an increased risk for stillbirth compared with uninfected women, and that the strength of this association was highest during the period of the SARS-CoV-2 B.1.617.2 (delta) variant predominance.[23]

Stillbirth can occur as a result of maternal infection with several viruses, collectively termed TORCH (an acronym for *Toxoplasma*, other, rubella, cytomegalovirus, herpes) agents, which include a variety of infectious agents including several new members and Ebola and Zika viruses.[24–26] In such cases, the mechanism leading to death typically results from transplacental passage of the virus following maternal viremia and placental involvement, culminating in fetal infection, intrauterine fetal demise, or neonatal death. Although it has now been established that SARS-CoV-2 can cause fetal deaths, the mechanism(s) remains largely unknown. To understand the cause(s) of fetal and neonatal demise following maternal infection from COVID-19, we analyzed 64 stillbirth and 4 neonatal death cases originating in 12 countries in which the placentas were proven to be infected with SARS-CoV-2.

MATERIALS AND METHODS

In this multinational case-based retrospective study the inclusion criteria were (1) women having a positive test result for SARS-CoV-2 during pregnancy using reverse transcriptase polymerase chain reaction (RT-PCR) prior to delivery; (2) an obstetric outcome of either stillbirth or early neonatal death; and (3) the placenta having been submitted for pathology examination and diagnosed with SARS-CoV-2 infection by PCR of placental tissues, direct visualization of fetal-derived placental cells using immunohistochemistry for SARS-CoV-2 antigens, RNA in situ hybridization for SARS-CoV-2 nucleic acid, fluorescence in situ hybridization (FISH), or a combination of these techniques.

For all 68 cases occurring from the 12 countries that comprised this study group, the perinatal pathologists, clinical specialists including obstetricians and pediatricians, and others involved with these patients were personally contacted by one of the authors (D.A.S.) for confirmation of the clinical, laboratory, and pathology findings. A unique and important aspect of this study was that the placentas were evaluated to determine the percentage of involve-

Table 1. Characteristics of Stillborn Fetuses and Placentas From Pregnant Women With SARS-CoV-2 Infection (Cases 1–12)

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5[98]
Maternal age, y	31	30	30	31	31[a]
Gestational age, wk	35 4/7	24 1/7	24 1/7	36 5/7	36 6/7 (twin 1)
Maternal RT-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive
Stillborn RT-PCR for SARS-CoV-2	Not performed	Not performed	Not performed	Weakly positive NP swab	Not performed
Transplacental transmission	Possible	Possible	Possible	Unlikely	Possible
Placenta weight, g	333[c]	Unknown	Unknown	473	517
Placental pathology findings	CHI MPFD TN IF FVM Infarcts Meconium Chronic deciduitis	CHI MPFD TN IF	CHI MPFD TN IF	CHI MPFD TN IF	CHI MPFD TN IF Fused dichorionic diamniotic twin placenta
Placental pathology involvement	>90% MPFD	80% MPFD	90% MPFD	80%	70%
Placental status for SARS-CoV-2	+IHC in STB +IHC in HC +IHC in VCE	+IHC in STB +IHC in intervillous histiocytes	+IHC in STB +IHC in intervillous histiocytes	+IHC in STB	+IHC in STB +IHC in CT
Autopsy pathology findings	Performed: aspiration; meconium in airways; thymic involution	Not performed	Not performed	Performed: minimal microvesicular steatosis	Performed: slight thymic involution
Stillborn organ staining for SARS-CoV-2	Not performed	Not performed	Not performed	IHC negative in lungs, liver, heart, kidneys	Not performed

Abbreviations: CHI, chronic histiocytic intervillositis; CT, cytotrophoblast; FVM, fetal vascular malperfusion; HC, Hofbauer cells; IF, increased fibrin; IHC, immunohistochemistry; ISH, RNA in situ hybridization; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; NP, nasopharyngeal; NSA, no significant abnormalities; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VCE, villous capillary endothelium; VIL, villitis.

[a] Mother with severe preeclampsia, and dichorionic diamniotic twin pregnancy. Twin 2 was live-born but died on day of life 5.
[b] Mother had insulin-dependent type 2 diabetes.
[c] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.
[d] Fifth percentile.

ment by destructive tissue elements of SARS-CoV-2 placentitis as previously identified and defined; these consisted of chronic histiocytic intervillositis, increased perivillous fibrin deposition including massive perivillous fibrin deposition (MPFD), and villous trophoblast necrosis.[27–29] Clinical data, laboratory testing, and pathologic data, including the results of autopsy (when performed), were collected on forms designed specifically for the study. All contributors approved of the clinical, laboratory, and diagnostic details of their cases as described in this report.

All data are listed in tabular format for stillbirth cases in Tables 1 through 6 and for neonatal deaths in Table 6. Basic maternal demographic data include age and gestational age at delivery. Significant maternal conditions not related to SARS-CoV-2 infection are noted and listed as table footnotes. To the best of our knowledge, all mothers in this cohort were unvaccinated. In the case of neonatal deaths, Apgar scores and the day of life during which death occurred are listed. The status of SARS-CoV-2 infection and results of laboratory testing for the coronavirus are listed for the mother, stillborn, or neonate where available.

Placentas were weighed and examined grossly, and multiple representative sections were taken on site. The major diagnoses were performed and recorded using routine hematoxylin and eosin–stained slides. The presence of SARS-CoV-2 was evaluated in the majority of placentas using immunohistochemistry for SARS-CoV-2 antigens. In a few cases, RNA in situ hybridization for viral messenger RNA or FISH evaluation for SARS-CoV-2 was performed. Evaluation of placentas was conducted in some cases using RT-PCR on tissues that were either fresh, flash frozen, or formalin fixed and paraffin embedded. All testing was conducted according to locally approved methods in the pathology department at the hospital site.

The extent of placental pathology involvement was estimated using a synthesis of findings based upon the gross inspection of the placenta that was confirmed thorough microscopic analysis of a minimum of 4 representative sections of placental parenchyma. The number of tissue blocks submitted exceeded the minimum recommended in the Amsterdam Placental Workshop Group Consensus Statement.[30] The pathologists in this study reported

Table 1. Extended						
Case 6	Case 7[99]	Case 8	Case 9	Case 10	Case 11	Case 12
32	23	37	39	24	29	38[b]
21	25 5/7	30 4/7	26	33	25 2/7	36
Positive	Positive	Positive	Positive	Positive	Positive	Positive
Not performed	Not performed	Not performed	Not performed	Nor performed	Not performed	Positive NP swab; deep bronchial swab negative
Possible	Possible	Possible	Possible	Possible	Unlikely	Possible
224	164	327	228	Unknown	119[c,d]	365[c]
CHI MPFD TN IF	CHI MPFD TN IF	CHI MPFD TN IF IVT Single umbilical artery	CHI MPFD TN IF Hemosiderin in decidua capsularis Subchorionic thrombus Intervillous hemorrhage	CHI MPFD TN IF	CHI MPFD TN IF VIL	CHI MPFD TN IF
80%	80%–90% MPFD	100% (TN)	>80 % total placental involvement	>80% total placental involvement	70% MPFD 60% CHI 50% TN	>90% total placental involvement
+IHC in STB +IHC in CT	+IHC in STB +ISH in STB	+ISH in STB	+ISH in STB	+ISH in STB	+RT-PCR of placental swab +RT-PCR of digested placental tissue +IHC in STB (spike and nucleoprotein) +ISH in STB	+IHC in STB
Not performed	Not performed; gross examination normal	Not performed; skin sloughing	Not performed	Not performed	Performed: NSA	Performed: NSA
Not performed	Not performed	Not performed	Not performed	Not performed	IHC and ISH negative in multiple organs	Not performed

the estimated percentage of placental involvement in 2 ways: either as a single percentage metric representing the combination of all destructive lesions, or as a metric that was specific for a given microscopic finding(s). Site pathologists estimated the placental tissue involvement as either a single figure or a range of percentages.

In those placentas that had previously had some aspect of the case published, the references were provided. Pathologists at all study sites adhered to the placental pathology diagnostic criteria recommended in the Amsterdam Placental Workshop Group Consensus Statement.[30] Because the diagnostic criteria for MPFD have varied among investigators, in this study a minimum of 30% of placental fibrin deposition in the characteristic pattern was necessary to make the diagnosis.

In all cases there was either approval received from the local institutional review boards or institutional waiver and parental permission obtained, and there was compliance with the Declaration of Helsinki for Human Research.

RESULTS

Analysis of SARS-CoV-2 Placentitis Abnormalities

SARS-CoV-2 placentitis, as defined by the coexistent occurrence of 3 microscopic findings—chronic histiocytic intervillositis, increased fibrin deposition, and trophoblast necrosis—was identified in 65 of 68 placentas (97%) in this study (Tables 1 through 6). Two of the 3 cases that did not have all 3 constituents of SARS-CoV-2 placentitis diagnosed (cases 42 and 46) were preterm deliveries (20 5/7 and 29 weeks, respectively) lacking chronic histiocytic intervillositis but having MPFD and trophoblast necrosis. The third case, case 60, did not have MPFD, but had massive recent infarcts and decidual vessel thrombi present together with trophoblast necrosis and chronic histiocytic intervillositis.

Increased fibrin deposition was diagnosed in all 68 placentas (100%) (Figures 1 through 3). Among 68 placentas with increased fibrin, MPFD was diagnosed in 63 cases (93%), not being diagnosed in cases 19, 20, 22, 31, and 60. In the 63 placentas having MPFD, it occurred together with trophoblast necrosis in all 63 cases (100%) and with chronic histiocytic intervillositis in 61 (98%) (Figures 4, A and B, and 5).

Chronic histiocytic intervillositis was present in 66 of 68 placentas (97%). It was not diagnosed in case 42, in which no other inflammatory process was present, and in case 46, which had 50% of placental involvement with villitis. Among the 66 placentas with chronic histiocytic intervillositis, 62 (94%) had concurrent MPFD.

Villous trophoblast necrosis was present in all 68 placentas (100%) from stillbirths and neonatal deaths.

Table 2. Characteristics of Stillborn Fetuses and Placentas From Pregnant Women With SARS-CoV-2 Infection (Cases 13–24)

Characteristic	Case 13[101]	Case 14[101]	Case 15[101]	Case 16[101]	Case 17[101]
Maternal age, y	31	26	25	25	37
Gestational age, wk	35 1/7	24 4/7	34 1/7	38 2/7	33
Maternal RT-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Negative but antibody test positive
Stillborn RT-PCR for SARS-CoV-2	Positive NP swab	Negative	Positive NP swab	Negative NP swab	Positive NP swab
Transplacental transmission	Possible	Unlikely	Possible	Possible	Unlikely
Placenta weight, g	Not performed	236	376	401[a]	305[a]
Placental pathology findings	CHI MPFD TN IF MVM Chorangiosis Calcifications	CHI MPFD (borderline) TN IF MVM	CHI MPFD TN IF	CHI MPFD TN IF Delayed villous maturation	CHI MPFD TN IF IVT MVM VIL
Placental pathology involvement	85%	25%–50%	>80 % MPFD	>80 % MPFD	>70% MPFD
Placental status for SARS-CoV-2	+IHC in STB	+IHC in STB	+ISH in STB	+IHC in STB	+IHC in STB
Autopsy pathology findings	Performed: thrombus in atrium and umbilical vein; epicardial petechiae	Performed: findings of intrauterine asphyxia	Not performed	Not performed	Performed: left hand malformation
Stillborn organ staining for SARS-CoV-2	IHC positive in lung tissue	Negative	Not performed	Not performed	Negative

Abbreviations: CHI, chronic histiocytic intervillositis; CNS, central nervous system; CT, cytotrophoblast; FFPE, formalin-fixed, paraffin-embedded; IF, increased fibrin; IHC, immunohistochemistry; ISH, RNA in situ hybridization; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; NP, nasopharyngeal; NSA, no significant abnormalities; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VIL, villitis.

[a] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.

Additional Placental Findings

Except for the findings that constitute SARS-CoV-2 placentitis, the most frequent pathology finding present in this cohort was intervillous thrombi or hemorrhages, present in 25 placentas (37%). Villitis was the next most frequent abnormality, occurring in 22 of 68 placentas (32%). These were followed by findings of maternal vascular malperfusion in 12 placentas (18%), antemortem fetal vascular malperfusion in 7 (10%), and acute chorioamnionitis in 9 (13%). Less common findings included placental infarcts, umbilical vessel thrombi, chorangiosis, and chronic chorioamnionitis.

There were 23 placentas that measured below the 10th percentile of weight stratified for gestational age.

Percentage Placental Involvement by SARS-CoV-2 Placentitis

In each placenta the contributing pathologist(s) carefully estimated the percentage of placental tissue involvement of representative sections for the destructive components of SARS-CoV-2 placentitis in correlation with the gross features of the placenta. These included intervillous fibrin deposition, chronic histiocytic intervillositis, and trophoblast necrosis. In some placentas a percentage range of placental involvement was provided, and in these cases the mean of the range of placental involvement was used in calculating the average placental involvement for the entire data set. Some cases estimated the percentage of placental involvement as greater than a specific number (for example >80%), and in these cases the stated percentage metric (for example 80%) was used.

Among the 68 placentas, the mean extent of tissue involvement by SARS-CoV-2 placentitis was 77.7%. Both the median and mode values for the extent of placental involvement were 80%, with a range between 35% and 100%. The interquartile range was 15%, with outliers of 35%, 37.5%, and 40%.

Identification of SARS-CoV-2 Involvement and Distribution in the Placenta

Among the 68 placentas from 64 stillborn fetuses and 4 neonatal deaths in this study, there were differing laboratory methods used to identify SARS-CoV-2 involvement of the placenta (Tables 1 through 6). All 68 placentas had at least 1 testing modality positive for SARS-CoV-2. The most frequent method used was immunohistochemical staining with antibody to SARS-CoV-2 antigen, which was per-

Table 2. Extended						
Case 18	Case 19[96]	Case 20[96]	Case 21[96]	Case 22[96]	Case 23[96]	Case 24[58]
26	38	24	32	34	37	26
37 5/7	37 4/7	27	28 1/7	31 4/7	20 2/7	34 5/7
Positive	Positive	Positive	Positive	Positive	Positive	Positive
Positive NP swab	Positive NP swab; lung, liver, and CNS samples negative	Negative	Not performed	Positive lung tissue	Not performed	Not performed
Possible	Unlikely	Unlikely	Possible	Unlikely	Unlikely	Possible
374[a]	590	126[a]	212	234[a]	105	366
CHI MPFD TN IF IVT MVM VIL	CHI TN IF	CHI TN IF	CHI MPFD TN IF	CHI TN IF	CHI MPFD TN IF	CHI MPFD TN IF IVT VIL
>80%	TN 97% CHI 50% IF 10%	TN 87% CHI 36% IF 29%	TN 83% CHI 34% MPFD 40%	TN 95% CHI 40% IF 10%	TN 65% CHI 50% MPFD 45%	>80% total placental involvement
+IHC in STB and CT	+IHC in STB +ISH in STB	+IHC in STB +ISH in STB	+IHC in STB +ISH in STB	+IHC in STB +ISH in STB	+IHC in STB +ISH in STB	+IHC in STB +RT-PCR from placental FFPE
Not performed; gross examination normal	Performed: Acute hypoxia findings; left renal agenesis	Performed: NSA	Not performed	Performed: acute hypoxia findings	Performed: NSA	Performed: NSA
Not performed	Not performed	Negative	Not performed	Negative	Negative	Not performed

formed in 53 of 68 placentas (78%), either alone or along with another type of testing. It was performed as the only test to detect SARS-CoV-2 in 38 of 68 placentas (56%). Immunohistochemistry was used in combination with other tests in 15 of 68 placentas (22%): together with RNA in situ hybridization in 6 placentas, in combination with PCR in 6 placentas, with FISH and PCR in 1 case, and with RNA in situ hybridization and PCR in 2 cases. RNA in situ hybridization (Figure 6) was used as the only test to detect SARS-CoV-2 placental involvement in 5 of 68 placentas (7%). PCR testing of fresh, frozen, or fixed placental tissues was performed as the sole test to detect SARS-CoV-2 in 10 of 68 placentas (15%).

The most common placental cell to be involved with SARS-CoV-2 was the syncytiotrophoblast, which stained positive in all 58 placentas (100%) in which testing was performed that could localize the virus to specific cell types. In a minority of cases there were additional cell types identified to be positive for the virus; these included cytotrophoblast in 7 of 58 placentas (12%), Hofbauer cells in 3 of 58 placentas (5%), villous stromal cells (not otherwise specified) in 3 of 58 placentas (5%), maternal cells (macrophages) in the intervillous space in 3 of 58 placentas (5%), villous capillary endothelial cells in 2 of 58 placentas (3%), and extravillous trophoblast in 1 placenta (2%).

Timing of Fetal and Neonatal Demise

Among the 64 stillborn fetuses in this study, death occurred at a mean gestational age of 30 weeks, with a modal value of 30 weeks 1 day. Delivery of the 64 stillbirths ranged from 15 to 39.2 weeks gestation. Eight stillbirth cases (13%) were delivered at full term (>37 weeks gestation).

The 4 cases of neonatal death were all delivered preterm at a mean gestational age of 30.8 weeks and survived for an average of 3.5 days following delivery.

Autopsy Pathology Findings

Autopsy examination was performed on 30 of the 68 cases (44%)—29 stillborns and 1 neonatal demise. The majority of the autopsies (19 of 30; 63%) revealed no fetal significant abnormalities. The most frequent pathologic findings that were identified related to intrauterine hypoxia and asphyxia, present in 5 cases (cases 13, 14, 19, 22, and 59). These findings of hypoxia included petechial hemorrhages in fetal organs, persistence of nucleated fetal red blood cells, and acute organ hemorrhages. There were 2 cases of thymic involution (cases 1 and 5) and 1 case each with aspiration of intrauterine contents (case 1), microvesicular steatosis (case 4), thrombosis of umbilical vein and atrium (case 13), hand malformation (case 17), unilateral renal agenesis (case 19), mild lymphocytic interstitial pulmonary infiltrates (case 61), and atelectasis with multiple organ hemorrhages (case 62). There were no gross or microscopic abnormalities identified in the 30 autopsies that related to significant tissue inflammation or necrosis that could be attributed to viral infection.

Table 3. Characteristics of Stillborn Fetuses and Placentas From Pregnant Women With SARS-CoV-2 Infection (Cases 25–36)					
	Case 25[91]	Case 26[91]	Case 27[91]	Case 28[91]	Case 29[91]
Maternal age, y	35	28	28	26[a]	36[a]
Gestational age, wk	24 3/7	33 5/7	20 3/7	30 1/7	32 5/7
Maternal RT-PCR for SARS-CoV-2	Positive[b]	Positive[b]	Positive[b]	Positive[b]	Positive[b]
Stillborn RT-PCR for SARS-CoV-2	Positive NP swab	Not detected from internal autopsy swab. NP swab not performed	Positive NP swab	Positive NP swab. Negative RT-PCR on lung	Negative RT-PCR on lung
Transplacental transmission	Possible	Possible	Possible	Unlikely	Unlikely
Placental weight, g	236	300[c]	126	394	630
Placental pathology findings	CHI MPFD TN IF	CHI MPFD TN IF ACA FTV: umbilical artery thrombus	CHI MPFD TN IF nRBCs in fetal circulation	CHI MPFD TN IF	CHI MPFD TN IF
Placental pathology involvement	>80%–90%	>80%–90%	>80%–90%	>80%–90%	>80%–90%
Placental status for SARS-CoV-2	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB
Autopsy pathology findings	Not performed; external examination only	Performed: NSA	Performed: NSA	Performed: NSA	Performed: NSA
Stillborn organ staining for SARS-CoV-2	Not performed	Not performed	Not performed	Not performed	Not performed

Abbreviations: ACA, acute chorioamnionitis; CHI, chronic histiocytic intervillositis; FTV, fetal thrombotic vasculopathy; HC, Hofbauer cells; IF, increased fibrin; IHC, immunohistochemistry; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; NP, nasopharyngeal; nRBCs, nucleated red blood cells; NSA, no significant abnormalities; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VCE, villous capillary endothelium; VIL, villitis.

[a] Mother with thrombocytopenia.
[b] Mother had SARS-CoV-2 alpha (B.1.1.7).
[c] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.

Identification of SARS-CoV-2 in the Stillborn Fetus and Neonate

Among all 68 fetuses and neonates in this study, SARS-CoV-2 was detected from a body specimen in 16 of 28 cases tested (57%). These included 10 cases in which the virus was identified by PCR of nasopharyngeal swabs alone, 2 cases having positive PCR and immunohistochemistry from multiple visceral organs, and 1 case each having positive nasopharyngeal, gastric, and mouth swabs; positive throat swab; positive PCR in a nasopharyngeal swab and lung tissue; and a positive PCR from a lung swab.

Intrauterine SARS-CoV-2 Transmission in Stillborn Fetuses

The World Health Organization criteria for evaluating intrauterine SARS-CoV-2 transmission in stillborn fetuses were used.[31] Intrauterine SARS-CoV-2 infection in the case of fetal demise requires both evidence of maternal SARS-CoV-2 infection anytime during pregnancy and detection of SARS-CoV-2 in fetal tissue, amniotic fluid, or placental specimens. In addition to positive maternal testing for SARS-CoV-2, the following criteria have been proposed to identify either confirmed, possible, or unlikely cases of maternal-fetal transmission. Confirmed maternal-fetal transmission requires fetal tissue from a sterile site to test positive for SARS-CoV-2 using either RT-PCR or in situ hybridization. Possible transmission can be evaluated using 2 sets of criteria. In those cases where the fetal tissue was not tested for SARS-CoV-2 via RT-PCR and in situ hybridization, there is possible transmission if one or more of the following tests are positive for SARS-CoV-2: (1) fetal tissue immunohistochemistry or microscopy or fetal swab RT-PCR; (2) amniotic fluid; and (3) placental tissue (RT-PCR, in situ hybridization, immunohistochemistry or microscopy) or placental swab RT-PCR. In cases where the fetal tissue was tested for SARS-CoV-2 using RT-PCR or in situ hybridization and was negative, possible transmission may have occurred if the amniotic fluid is positive for SARS-CoV-2. Unlikely transmission criteria include fetal tissue testing negative for SARS-CoV-2 by RT-PCR or in situ hybridization together with one or more of the following tests being positive for SARS-CoV-2: fetal tissue immunohistochemistry or microscopy or a fetal swab RT-PCR, or placental tissue (RT-PCR, in situ hybridization, immunohistochemistry or microscopy) or placental swab RT-PCR. These criteria are not optimal, as they do not address the significance of negative immunohistochemical staining of fetal organs for SARS-CoV-2 in the absence of additional tissue analysis using RNA in situ hybridization staining or PCR. Thus, for the purposes of this study, we consider that negative staining of fetal organs for SARS-CoV-2 using immunohistochemistry makes maternal-fetal transmission unlikely in the absence of molecular testing of these organs.

Table 3. Extended						
Case 30	Case 31	Case 32	Case 33	Case 34	Case 35	Case 36
24	31	37	34	26	27	39
35 5/7	37 2/7	27 4/7	22 4/7	39 1/7	15	36
Positive	Positive	Positive	Positive	Positive	Positive	Positive
Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
Possible	Possible	Possible	Possible	Possible	Possible	Possible
340[c]	293[c]	236	165	328[c]	50	294[c]
CHI MPFD TN IF	CHI IF TN	CHI MPFD IF TN IVT	CHI MPFD IF TN ACA	CHI MPFD IF TN IVT VIL	CHI MPFD IF TN IVT	CHI MPFD IF TN IVT VIL
>90% MPFD	>30%–50%	MPFD >80% CHI >50%	MPFD >70%	MPFD >70% CHI >50%	MPFD >70% CHI >40%	>70% MPFD
+IHC in STB +IHC in HC +IHC in VCE	+IHC in STB +qPCR	+IHC in STB +qPCR	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB
Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed

Applying the World Health Organization criteria and our caveats to these data and considering that all mothers and placentas were positive for SARS-CoV-2, the results of fetal organ testing were the determining covariable in assessing the likelihood of maternal-fetal transmission. Among the 64 stillbirths, maternal-fetal transmission of SARS-CoV-2 was confirmed in 2 cases (cases 47 and 61), possible in 49 cases, and unlikely in 13 cases. In the 4 cases of neonatal death, 3 cases had possible in utero transmission and in 1 case it was unlikely. There were no clinical or pathologic findings that viral infection of fetal tissues had any significant role in causing a fetal or neonatal death in this cohort.

DISCUSSION

Even prior to the COVID-19 pandemic, stillbirth was a persistent global public health problem. As a result of deficiencies and inconsistencies in the global surveillance and reporting of stillbirths, the number that occur annually is unknown, but it has been estimated to be between 2 and 6 million.[32]

Maternal infections with infectious agents, especially those of the TORCH group, can result in placental infection and transmission of the agent to the fetus that results in pathologic changes to organs causing stillbirth or neonatal death.[33–36] A major concern at the start of the COVID-19 pandemic was the effect of the virus on pregnant women and their offspring.[2,37–39] Placental pathology has been useful in the understanding of maternal-fetal infection and adverse obstetric outcomes with previous emerging infections, but early studies from mothers with SARS-CoV-2 infection were inconclusive, as the majority of placentas came from newborns and placentas that tested negative for SARS-CoV-2 infection.[37–41] In examining a series of placentas that were found to be positive for SARS-CoV-2 using immunohistochemistry or RNA in situ hybridization, Schwartz and Morotti[27] found that placentas infected with the virus had a significantly different pattern of pathologic findings than did uninfected placentas, regardless of the infection status of the neonate. Additional studies[40–48] found that placentas testing positively for SARS-CoV-2 were typically characterized by a spectrum of destructive findings that included villous trophoblast necrosis, chronic histiocytic intervillositis, and increased fibrin up to the level of MPFD. A study of 11 stillborn and live-born babies having placental involvement with SARS-CoV-2 confirmed that the microscopic findings present in these cases were risk factors for intrauterine viral transmission and perinatal morbidity and mortality.[29] When occurring in a placenta delivered from a mother with COVID-19, the triad of findings of histiocytic intervillositis, perivillous fibrin deposition, and trophoblast necrosis has been termed SARS-CoV-2 placentitis.[28]

Placental abnormalities are the leading identifiable cause of stillbirth.[49–51] As a result, pathology examination of the placenta is a critically important tool for the determination of the cause of perinatal mortality.[52–54] Placental disease can cause malperfusion that results in placental insufficiency and stillbirth.[50,55,56] In this present study, we have documented a consistent pattern of abnormalities from 68 placentas having confirmed SARS-CoV-2 involvement that were associated with stillbirths and/or neonatal deaths. The major pathology lesions that were present—fibrin deposition, trophoblast necrosis, and chronic histiocytic intervillositis—are all destructive lesions that are associated with SARS-CoV-2 maternal infection.[29,57–60] These placental abnormalities can, when occurring by themselves, have deleterious effects of placental function, and recent research suggests that they

Table 4. Characteristics of Stillborn Fetuses and Placentas From Pregnant Women With SARS-CoV-2 Infection (Cases 37–48)						
	Case 37	Case 38	Case 39	Case 40	Case 41	Case 42
Maternal age, y	39	34	31	38	39	27
Gestational age, wk	31 1/7	29	29 1/7	30 1/7	31	20 5/7
Maternal RT-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Positive
Stillborn RT-PCR for SARS-CoV-2	Not performed	Not performed	Not performed	Positive throat swab	Not performed	Not performed
Transplacental transmission	Possible	Possible	Possible	Possible	Possible	Possible
Placenta weight, g	450	210[a]	183[a]	262	450	270
Placental pathology findings	CHI MPFD TN IF IVT VIL	CHI MPFD TN IF IVT VIL	CHI MPFD TN IF IVT	CHI MPFD TN IF IVT	CHI MPFD TN IF IVT	MPFD TN IF IVT
Placental pathology involvement	>70% MPFD	>70% MPFD	50% MPFD	60%–70% MPFD 60%–70% CHI	>30%–40%	>70%
Placental status for SARS-CoV-2	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB
Autopsy pathology findings	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed
Stillborn organ staining for SARS-CoV-2	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed

Abbreviations: ACA, acute chorioamnionitis; CHI, chronic histiocytic intervillositis; CT, cytotrophoblast; FFPE, formalin-fixed, paraffin-embedded; FVM, fetal vascular malperfusion; IF, increased fibrin; IHC, immunohistochemistry; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; NP, nasopharyngeal; NSA, no significant abnormalities; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VIL, villitis.

[a] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.

can occur independent of the severity of maternal infection.[58]

All 68 of the placentas in this cohort were demonstrated to be positive for SARS-CoV-2 using either molecular or immunohistochemical methods. In those placentas where the virus was localized using either immunohistochemistry or RNA in situ hybridization, the syncytiotrophoblast was involved in all cases. Previous studies have indicated that although the syncytiotrophoblast is the most common placental cell type to be involved with SARS-CoV-2,[59] other villous cells, including cytotrophoblasts,[61] Hofbauer cells,[60] and endothelial cells,[60] can also stain positively for the virus. In our series, cytotrophoblasts, Hofbauer cells, and villous stromal and endothelial cells were occasionally found to stain positively for SARS-CoV-2.

The most frequent abnormality in this cohort of placentas was abnormally increased fibrin deposition, occurring in 100% of cases including stillborn fetuses and neonatal deaths. Fibrin deposits occur in placentas under normal circumstances to a certain degree, and are found beneath the chorionic plate, in the intervillous space and adjacent to chorionic villi, and at the basal plate. In pathologic conditions, a spectrum of placental disorders characterized by an abnormal increase in fibrin can develop; these include increased fibrin deposition, fibrinoid plaque, infarcts, and the 2 most severe abnormalities, MPFD and maternal floor infarction.

MPFD is a highly unusual abnormality characterized by an excessive deposition of fibrin/fibrinoid material in the intervillous space. The fibrin/fibrinoid obstructs normal perfusion and gas-nutrient exchange and entraps the chorionic villi, resulting in villous ischemia and necrosis that causes placental insufficiency.[62–64] Long before the COVID-19 pandemic, MPFD had been recognized as a cause of perinatal morbidity and mortality due to fetal hypoxic injury that included spontaneous abortion, intrauterine growth restriction, preterm delivery, stillbirth, neonatal death, neurologic disease in surviving infants, and significant recurrence risk.[62–66] Cases of MPFD have been described in which autopsy pathology indicated that the cause of death was from placental insufficiency.[63] The published diagnostic criteria for MPFD have been variable, ranging from a high of 50% involvement[67] to a lower percentage of involvement of greater than 20% and 25%.[68–70] In this present report, we used a criterion of fibrin deposition of 30% or greater in a characteristic pattern for MPFD. Using this criterion, MPFD was present in 63 of the 68 placentas (94%) in this study. In all 63 of these cases (100%), it coexisted with at least 1 other placental finding of SARS-CoV-2 placentitis. Trophoblast necrosis was univer-

Table 4. Extended					
Case 43[58]	Case 44[58]	Case 45	Case 46	Case 47[102]	Case 48
33	30	27	17	33	38
30	22 4/7	32	29	34 4/7	38
Positive	Positive	Positive	Positive	Positive	Positive
Not performed	Not performed on fetus +PCR of amniotic fluid	Positive NP swab	Not performed	Positive in umbilical cord, salivary gland; trachea; olfactory bulb; lungs; liver and kidney	Not performed
Possible	Possible	Possible	Possible	Confirmed	Possible
255	105[a]	340	340	470	256
CHI MPFD IF TN IVT VIL	CHI MPFD IF TN IVT VIL	CHI MPFD TN IF MVM Chronic chorioamnionitis Decidual hemorrhage	MPFD TN IF VIL FVM with fetal thrombotic vasculopathy	CHI MPFD IF TN IVT MVM FVM VIL ACA (slight)	CHI MPFD TN IF IVT MVM FVM VIL ACA (slight)
>80% total placental involvement	>80% total placental involvement	>50% TN >50% MPFD 30% CHI 15% IF	50% VIL 30% IF 30% FVM 20% TN	MPFD >80% CHI >50%	MPFD >80% CHI >60%
+IHC in STB +RT-PCR of placental FFPE	+IHC in STB	+RT-PCR Staining not performed	+RT-PCR Staining not performed	+RT-PCR of fresh tissue Staining not performed	+IHC in STB, CT, stromal cells +RT-PCR of fresh tissue
Performed: NSA	Performed: NSA	Not performed	Not performed	Performed: NSA; maceration	Not performed
Not performed	Not performed	Not performed	Not performed	+IHC in lung, brain, and heart	Not performed

sally present in placentas having MPFD. In 61 of the 63 placentas (98%) with MPFD, chronic histiocytic intervillositis was also present.

Chronic histiocytic intervillositis occurred in 97% of the placentas in this cohort, but prior to the COVID-19 pandemic it was rarely seen and had an unknown etiology since it was first described by Labarrere and Mullen[71] in 1987. It was found to be associated with a high recurrence rate and adverse pregnancy outcomes that included miscarriage, intrauterine fetal demise, preterm birth, and intrauterine growth restriction.[71–73] Its exact prevalence is unknown, but it was believed to occur in approximately 6 of 10 000 second- and third-trimester placentas (0.6%) prior to the COVID-19 pandemic.[72,74] Chronic histiocytic intervillositis is characterized by the accumulation of mononuclear inflammatory cells (predominantly histiocytes) in the intervillous space of the placenta, and may be accompanied by lymphocytes and occasionally neutrophils.[75] Chronic histiocytic intervillositis was noted to occur together with MPFD before the COVID-19 pandemic,[75–77] where it resulted in either intrauterine fetal demise or a pregnancy termination. In cases of SARS-CoV-2 placentitis it may be misleading to retain the term *chronic* in describing this intervillositis, as the development of placental pathology appears not to be long in duration. In our study, all 66 placentas with chronic histiocytic intervillositis had increased fibrin deposition, and 94% had concurrent MPFD.

Foremost among other pathology abnormalities identified were intervillous thrombi, occurring in 37% of placentas. Intervillous thrombi are not typically associated with adverse birth outcomes unless they are large or multiple; however, in placentas that are already compromised because of the destructive effects of SARS-CoV-2 placentitis, they likely exacerbate the malperfusion. Roberts and colleagues (written communication, December 2021) recently found parenchymal thrombohematomas (intervillous thrombi or hemorrhages) to be associated with SARS-CoV-2 placentitis and stillbirth. Among our cohort of 68 placentas, villitis occurred in 22 (32%). In all cases but 1, villitis was present together with chronic histiocytic intervillositis, and it remains to be determined exactly what the relationship is between these 2 inflammatory conditions.

In understanding the combined effects of the abnormalities that constitute SARS-CoV-2 placentitis in producing placental insufficiency, it is important to remember that studies conducted prior to the COVID-19 pandemic demonstrated a direct relationship between the number of placental abnormalities in any given placenta and the development of perinatal morbidity and mortality, arguing for a synergistic effect among multiple lesions.[78,79] This phenomenon is well illustrated in SARS-CoV-2 placentitis, which, unlike placental infection from other TORCH agents, constitutes a simultaneous grouping of destructive placental lesions occurring in the same pregnancy. After examination of the microscopic effects of SARS-CoV-2 placentitis on the placental tissues, it is apparent that these lesions can result in obstruction of maternal and fetal blood flow through the placenta, as well as causing irreversible damage and necrosis of placental tissues and reduction of the functional capacity

Table 5. Characteristics of Stillborn Fetuses and Placentas From Pregnant Women With SARS-CoV-2 Infection (Cases 49–61)

	Case 49	Case 50	Case 51	Case 52[29]	Case 53	Case 54
Maternal age, y	34	25	25	32	30	32
Gestational age, wk	28	32	30	39 2/7	30 6/7	28 3/7
Maternal RT-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Positive
Stillborn RT-PCR for SARS-CoV-2	Negative in paraffin-embedded blocks	Not performed	Not performed	NP swab negative	Not performed	Not performed
Transplacental transmission	Unlikely	Possible	Possible	Possible	Possible	Possible
Placenta weight, g	220	307	198[b]	350[b]	201[b]	123[b]
Placental pathology findings	CHI MPFD TN IF IVT MVM FVM VIL	CHI MPFD TN IF IVT MVM FVM VIL	CHI MPFD TN IF IVT MVM FVM VIL ACA (slight)	CHI MPFD TN IF MVM Atherosis Accelerated villous maturation Infarcts	CHI MPFD TN IF VIL ACA Deciduitis	CHI MPFD TN IF VIL ACA
Placental pathology involvement	MPFD >80% CHI >60%	MPFD >80% CHI >60%	MPFD >80% CHI >50%	MPFD 70%–80% CHIV 10%	>90% MPFD	>90% MPFD >90% TN
Placental status for SARS-CoV-2	+RT-PCR of fresh tissue Staining not performed	+RT-PCR of fresh tissue Staining not performed	+RT-PCR of fresh tissue Staining not performed	+IHC in STB +FISH in STB +RT-PCR of flash frozen tissue	+RT-PCR of digested placental tissue	+RT-PCR of digested placental tissue
Autopsy pathology findings	Performed; small for gestational age fetus; maceration	Not performed	Not performed	Not performed	Not performed	Not performed
Stillborn organ staining for SARS-CoV-2	Not performed	Not performed	Not performed	Not performed	Not performed	Not performed

Abbreviations: ACA, acute chorioamnionitis; CHI, chronic histiocytic intervillositis; CT, cytotrophoblast; FFPE, formalin-fixed, paraffin-embedded; FISH, fluorescence in situ hybridization; FVM, fetal vascular malperfusion; HC, Hofbauer cells; IF, increased fibrin; IHC, immunohistochemistry; ISH, RNA in situ hybridization; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; NP, nasopharyngeal; NSA, no significant abnormalities; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VIL, villitis.

[a] Mother had multiorgan thromboembolic disease including pelvic organs and pulmonary embolism.
[b] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.
[c] RT-qPCR result positive for SARS-CoV-2 genotype 20H/501Y. V2 (B1.351, beta) variant.

of the tertiary villous capillary bed, leading to significant malperfusion and placental insufficiency.

Perhaps the most important finding in this study relates to the degree of involvement of the placentas from the destructive lesions that constitute SARS-CoV-2 placentitis. The average placenta in this cohort had 77.7% involvement with SARS-CoV-2 placentitis. This extent of placental damage and consequent malperfusion is striking, and far exceeds the degree of placental involvement and destruction that is typically seen with other viral TORCH agents. At these high levels of placental damage, the placenta cannot function at the level necessary to provide sufficient oxygen and nutrients to the fetus to sustain life. In examining the results of this study, and in consideration of not only the destructive nature of the individual placental abnormalities of SARS-CoV-2 placentitis but also the occurrence of additional placental pathology findings including intervillous thrombi, villitis, and maternal vascular malperfusion, it can be reasonably concluded that placental insufficiency was occurring together with fetal hypoxia, which produced a hypoxic-ischemic fetal or early neonatal demise. Among these 68 cases of stillbirth and neonatal death, there were no other significant potential etiologies identified for perinatal demise from either a clinical or pathologic perspective.

Table 5. Extended

Case 55	Case 56	Case 57	Case 58	Case 59 [95]	Case 60	Case 61[93]
26	35	36	36	40	35[a]	32
28 2/7	34	22 5/7 (twin 1)	22 5/7 (twin 2)	24 2/7	28	38
Positive	Positive	Positive	Positive	Positive	Positive	Positive
Not performed	Not performed	Not performed	Not performed	NP, gastric and mouth swabs positive	Negative from lung and spleen	NP tissue positive
Possible	Possible	Possible	Possible	Possible	Unlikely	Confirmed
295	331	118	115	204	206[b]	480
CHI MPFD TN IF	CHI MPFD TN IF	CHI MPFD TN IF Dichorionic diamniotic twin placenta	CHI MPFD TN IF Dichorionic diamniotic twin placenta	CHI MPFD TN IF IVT	CHI TN IF IVT Massive fresh infarcts Decidual vessel thrombi	CHI MPFD TN IF VIL
80% MPFD	80% MPFD	80% MPFD	80% MPFD	MPFD >80 % CHI 70 %	>90% infarcts <5% CHI, IF, TN, IVT	70%
+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB	+IHC in STB, CT, HC, stromal and extravillous trophoblast cells +RT-PCR of frozen and FFPE tissue[c]	+IHC in STB, villous stromal cells and cells in intervillous space	+IHC in STB +ISH in STB and intervillous cells +qPCR in FFPE
Performed: NSA	Performed: NSA	Performed: NSA	Performed: NSA	Performed: mild growth restriction hypoxic lesions including petechial hemorrhages	Performed: hypoxic lesions	Performed: NSA; mild interstitial lymphocytic infiltrates in lung
Not performed	Not performed	Not performed	Not performed	Not performed	Not performed	+IHC in lung and kidney +ISH in lung +qRT-PCR in fresh tissues from lung, umbilical cord, and NP

The extent of placental damage and the nature of the pathology findings in these cases leads to questions regarding the timing of these processes and their terminology. Both increased fibrin and MPFD have not previously been considered to represent acute pathology processes and were believed to develop long before labor and delivery, based upon several factors including morphology, extent and severity of the disease process, and association with intrauterine growth restriction.[62,80] The occurrence of chronic histiocytic intervillositis was also consistent with a pathologic process of some duration. However, when it occurs with COVID-19 there are data that indicate a more accelerated process, as nearly all reported infections (based on onset of symptoms or date of positive COVID-19 test) occur within approximately 2 weeks or less of the diagnosis or delivery of the stillbirth.[28,58,80–82] We believe that our pathology data are strongly suggestive of a process that is occurring during a period ranging from several days up to 2 weeks after onset of maternal symptoms or positive COVID-19 testing. Because of this, it may be appropriate to use the term *histiocytic intervillositis* in place of *chronic histiocytic intervillositis* in these cases. In addition, we recommend that pregnant women with an acute SARS-CoV-2 infection be closely monitored for those first 2 to 3 weeks for fetal well-being to hopefully avoid intrauterine fetal demise.

The findings in the present study have additional important clinical ramifications. Placental insufficiency was the apparent cause of fetal and neonatal demise among these 68 cases. Although there are no standard criteria or agreed-upon consensus for the diagnosis of placental insufficiency,[83] it is generally agreed that it represents a pathologic process where there is ongoing and continual deterioration in placental functioning, resulting in decreasing transfer of maternal-derived oxygen and nutrients to the fetus through the placenta, resulting in intrauterine fetal hypoxia, hypoxemia, and acidosis.[83–86] In contrast to many other TORCH agents, our cases did not demonstrate evidence that the SARS-CoV-2 virus was causing mortality by inducing fetal somatic organ damage following placental

Table 6. Characteristics of Stillborn Fetuses (Cases 62–64), Neonatal Deaths (Cases 65–68), and Placentas From Pregnant Women With SARS-CoV-2 Infection

	Case 62[103]	Case 63[103]	Case 64[104]	Case 65[101]	Case 66[101]	Case 67[98]	Case 68
Maternal age, y	32	30	27[a]	30	31[b]	31[c]	35
Gestational age, wk	28 3/7	30 6/7	25 5/7	24 1/7	34	36 6/7 Twin 2	28 5/7
Maternal RT-PCR for SARS-CoV-2	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Newborn RT-PCR for SARS-CoV-2	Not performed	Not performed	Negative in liver	Negative	Negative	Not performed	Not performed
Transplacental transmission	Unknown	Unknown	Unlikely	Unlikely	Unknown	Unknown	Unknown
Placenta weight, g	123[d]	201[d]	215	156	400	517	238
Placental pathology findings	CHI MPFD TN IF VIL ACA	CHI MPFD TN IF VIL ACA Deciduitis	CHI MPFD TN IF IVT	CHI MPFD TN IF Infarcts	CHI MPFD TN IF IVT MVM VIL	CHI MPFD TN IF Dichorionic diamniotic fused twin placenta	CHI MPFD TN IF MVM (accelerated villous maturation)
Placental pathology involvement	>90% MPFD >90% TN	>90% MPFD >90% TN	>90% MPFD	90% MPFD	>90% MPFD	70%	80%
Placental staining for SARS-CoV-2	Placental tissue positive by RT-PCR No staining performed	Placental tissue and amniotic fluid positive by RT-PCR No staining performed	+ISH in STB and CT	+IHC in STB	+IHC in STB	+IHC in STB +IHC in CT	+IHC in STB
Autopsy pathology findings	Not performed	Not performed	Performed: NSA	Performed: intrauterine growth restriction; atelectasis. Pulmonary and adrenal hemorrhage; intraventricular and subarachnoid hemorrhage	Not performed; newborn had hypoxic ischemic encephalopathy	Not performed; imaging with severe hypoxic brain damage	Not performed
Stillborn organ staining for SARS-CoV-2	Not performed	Not performed	ISH negative in brain	Negative	Not performed	Not performed	Not performed
Death-to-delivery interval	Not applicable	Not applicable	Not applicable	Death on day of life 1	Death on day of life 8	Death on day of life 5	Death 11 min after delivery
Apgar score (min after birth)	Not applicable	Not applicable	Not applicable	2 (1), 5 (5), 7 (10)	0 (1), 0 (5), 1(10)	1 (1), 4 (5)	1 (1), 2 (5), 2 (10)

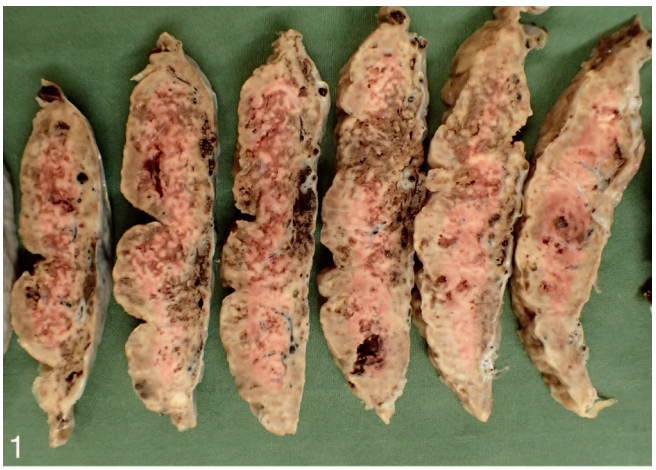
Abbreviations: ACA, acute chorioamnionitis; CHI, chronic histiocytic intervillositis; CT, cytotrophoblast; IF, increased fibrin; IHC, immunohistochemistry; ISH, RNA in situ hybridization; IVT, intervillous thrombi; MPFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion; NSA, no significant abnormalities; RT-PCR, reverse transcription polymerase chain reaction; STB, syncytiotrophoblast; TN, trophoblast necrosis; VIL, villitis.

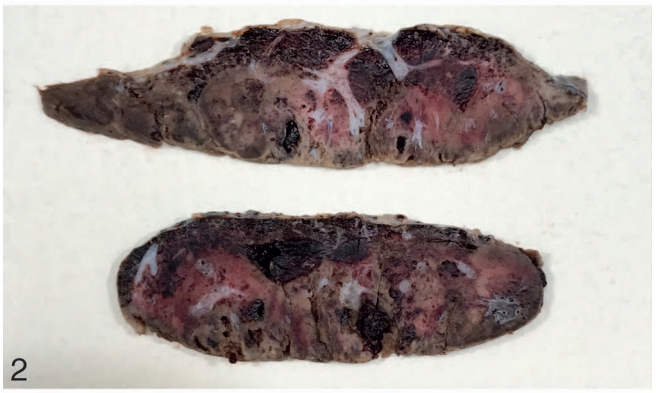
[a] Mother with severe preeclampsia and dichorionic diamniotic twin pregnancy. Twin 2 was live-born but died on day of life 5.
[b] Mother with severe preeclampsia, thrombocytopenia, and dichorionic diamniotic twin pregnancy.
[c] Mother with severe preeclampsia and dichorionic diamniotic twin pregnancy.
[d] Placental weight stratified for gestational age was less than the 10th percentile based on values in Pinar H, Sung CJ, Oyer CE, Singer DB.[100] Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907.

infection and transplacental transmission. Instead, the tissue damage appeared to be confined to the placenta, where it was extensive and highly destructive. Given the nature and extent of the placental injury and the technologic improvements in noninvasive obstetric diagnostic methods, it may be possible that obstetric ultrasound could be used for screening in those mother-fetus dyads at risk. Doppler ultrasound including superb microvascular imaging has been demonstrated to be a useful method for evaluating both fetal and placental circulations, and magnetic resonance imaging of the placenta using advanced methods such as T2-weighted rapid acquisition with relaxation enhancement imaging has been used to detect placental vascular abnormalities, including hemorrhages and infarctions.[87–90] An additional clinical consideration arises with the improvement in methods for vaccination and specific antiviral treatments. As our study indicates that the major cause of perinatal deaths among fetuses and neonates having placentas compromised by SARS-CoV-2 is placental insufficiency, and not direct viral infection of the fetal organs, reducing maternal SARS-CoV-2 viral burden through either immunization or antiviral therapy could conceivably decrease the risk of developing SARS-CoV-2 placentitis.

This study has several limitations, most of which were inherent in conducting a large retrospective clinical and pathologic investigation involving multiple geographically dispersed study sites and investigators. Protocols used for the clinical evaluation of mothers with COVID-19 were not uniform, although all clinicians in this study were experienced in the care and management of pregnant women having COVID-19. The nature of this study precluded providing detailed maternal clinical histories, but when significant maternal disease was present that was not related to COVID-19 it is listed as a table footnote, and no mothers had severe disease requiring intensive care or mechanical ventilation. There was also expected site-to-site variation in some laboratory methods, sampling of the placentas, and performance of immunohistochemical and molecular diagnostic methods at the different study locations in 12 countries. However, all testing was performed in accredited laboratories and in accordance with approved practices. Interobserver pathology diagnosis was minimized because all pathologists involved in this study either were experienced perinatal, pediatric, or placental pathologists or had a special interest in this field, and all adhered to diagnostic criteria from the Amsterdam Placental Workshop Group Consensus Statement.[30] This system is used globally and has become the standard basis for clinical and research activities in the field. Because of the large sample size of placentas and autopsies, an exhaustive listing of the minor pathology findings could not be provided, and only the relevant diagnoses are listed.

Our data from these 68 cases support previous case reports suggesting that placental insufficiency is responsible for perinatal deaths occurring with SARS-CoV-2 placentitis.[58,91–97] In summary, we found that SARS-CoV-2 placentitis can cause extensive placental damage as a result of destructive lesions, and that the damage can be further exacerbated by additional pathology abnormalities. Increased fibrin and MPFD, chronic histiocytic intervillositis, and trophoblast necrosis result in sizable destruction of the villous capillary bed accompanied by obstruction of the intervillous space, causing placental malperfusion and insufficiency that are incompatible with intrauterine survival. The fetal hypoxia that ensues can lead to a hypoxic-ischemic fetal demise or neonatal death. It is very fortunate that this sequence of events develops in only a small percentage of pregnant women having COVID-19.





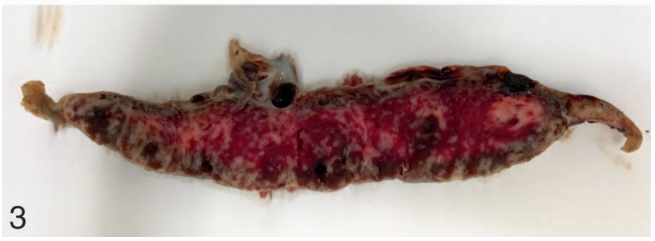


Figure 1. *Serially sectioned placenta from case 62 showing appearance of SARS-CoV-2 placentitis. Microscopic examination showed massive perivillous fibrin deposition, chronic histiocytic intervillositis, and trophoblast necrosis. The extent of pathology resulting from these destructive lesions was greater than 90% and led to placental insufficiency and stillbirth.*

Figure 2. *Gross pathology appearance of massive perivillous fibrin deposition that occurred with SARS-CoV-2 placentitis from a stillborn fetus. Intervillous thrombohematomas can be seen.*

Figure 3. *Sectioned placental specimen from case 61 illustrating SARS-CoV-2 placentitis. There was 70% involvement of placental tissue with this destructive process.*

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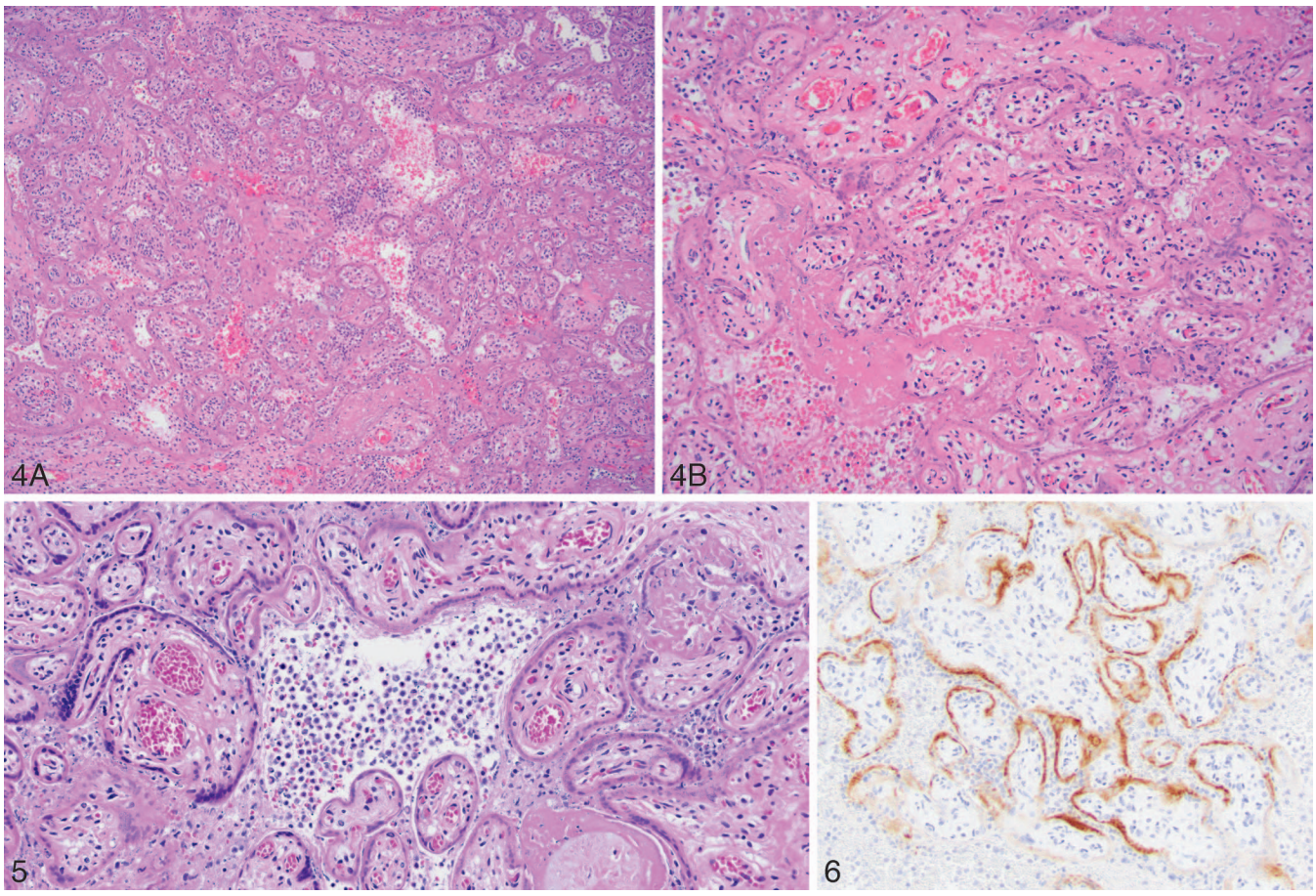

Figure 4. *A and B, Placenta from a stillborn fetus demonstrating the features of SARS-CoV-2 placentitis including massive perivillous fibrin deposition, chronic histiocytic intervillositis, and syncytiotrophoblast necrosis (hematoxylin-eosin, original magnifications ×4 [A] and ×10 [B]).*

Figure 5. *An area of intervillositis in a placenta from a stillborn fetus (case 64). This placenta also had massive perivillous fibrin deposition and necrosis of the syncytiotrophoblast (hematoxylin-eosin, original magnification ×20).*

Figure 6. *Placenta from a stillbirth (case 9) demonstrating positive staining for SARS-CoV-2 in the syncytiotrophoblast using RNA in situ hybridization (original magnification ×20).*

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