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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

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• **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 intervillitis. 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 intervillitis; 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 intervillitis, 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 ^e
CHI	CHI	CHI	CHI	CHI	CHI	CHI
MPFD	MPFD	MPFD	MPFD	MPFD	MPFD	MPFD
TN	TN	TN	TN	TN	TN	TN
IF	IF	IF	IF	IF	IF	IF
		IVT Single umbilical artery	Hemosiderin in decidua capsularis Subchorionic thrombus Intervillous hemorrhage		VIL	
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 intervillitis, 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 intervillitis 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 intervillitis.

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 intervillitis in 61 (98%) (Figures 4, A and B, and 5).

Chronic histiocytic intervillitis 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 intervillitis, 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 intervillitis; 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 intervillitis, 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-

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	CHI	CHI	CHI	CHI	CHI	CHI
MPFD	TN	TN	MPFD	TN	MPFD	MPFD
TN	IF	IF	TN	IF	TN	TN
IF			IF		IF	IF
IVT						IVT
MVM						VIL
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 intervillitis; 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	CHI	CHI	CHI	CHI	CHI	CHI
MPFD	IF	MPFD	MPFD	MPFD	MPFD	MPFD
TN	TN	IF	IF	IF	IF	IF
IF		TN	TN	TN	TN	TN
		IVT	ACA	IVT	IVT	IVT
				VIL		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 Morotti²⁷ 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 intervillitis, 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 intervillitis, 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 intervillitis—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 intervillitis; 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, intra-uterine 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% involvement⁶⁷ 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	CHI	CHI	MPFD	CHI	CHI
MPFD	MPFD	MPFD	TN	MPFD	MPFD
IF	IF	TN	IF	IF	TN
TN	TN	IF	VIL	TN	IF
IVT	IVT	MVM	FVM with fetal thrombotic vasculopathy	IVT	IVT
VIL	VIL	Chronic chorioamnionitis Decidual hemorrhage		MVM FVM VIL ACA (slight)	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 intervillitis was also present.

Chronic histiocytic intervillitis 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 Mullen⁷¹ 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 intervillitis 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 intervillitis 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 intervillitis, as the development of placental pathology appears not to be long in duration. In our study, all 66 placentas with chronic histiocytic intervillitis 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 intervillitis, 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 Atherosclerosis 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 intervillitis; 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	CHI	CHI	CHI	CHI	CHI	CHI
MPFD	MPFD	MPFD	MPFD	MPFD	TN	MPFD
TN	TN	TN	TN	TN	IF	TN
IF	IF	IF	IF	IF	IVT	IF
		Dichorionic diamniotic twin placenta	Dichorionic diamniotic twin placenta	IVT	Massive fresh infarcts Decidual vessel thrombi	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 intervillitis 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 intervillitis* in place of *chronic histiocytic intervillitis* 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 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 intervillitis, 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 surviv-

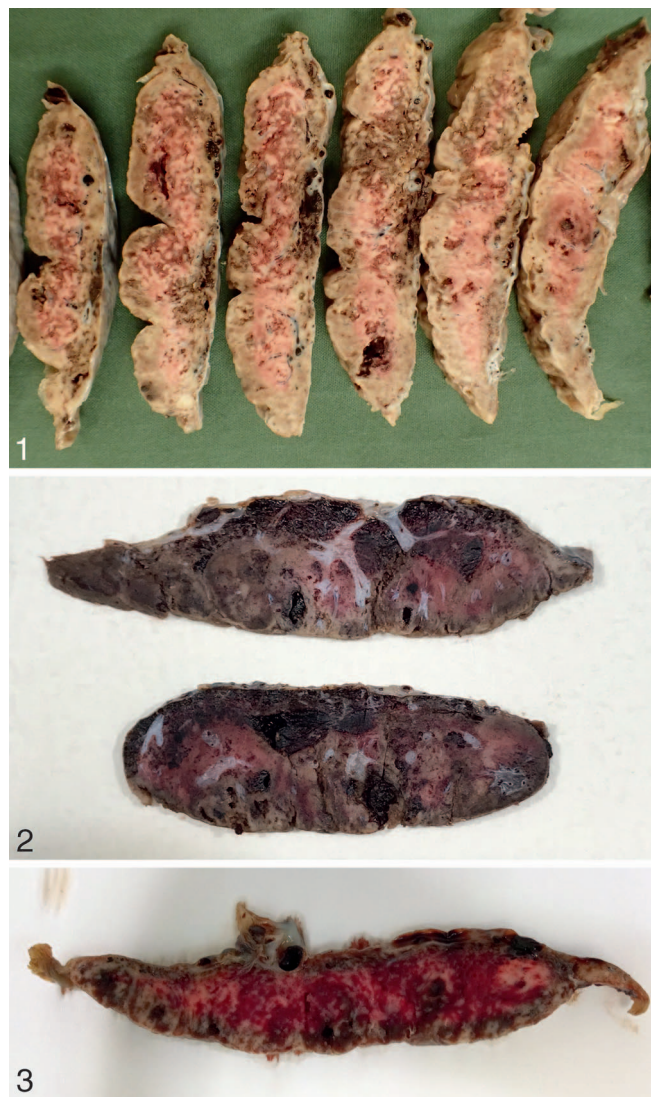


Figure 1. Serially sectioned placenta from case 62 showing appearance of SARS-CoV-2 placentitis. Microscopic examination showed massive perivillous fibrin deposition, chronic histiocytic intervillitis, and trophoblast necrosis. The extent of pathology resulting from these destructive lesions was greater 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.

al. 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.

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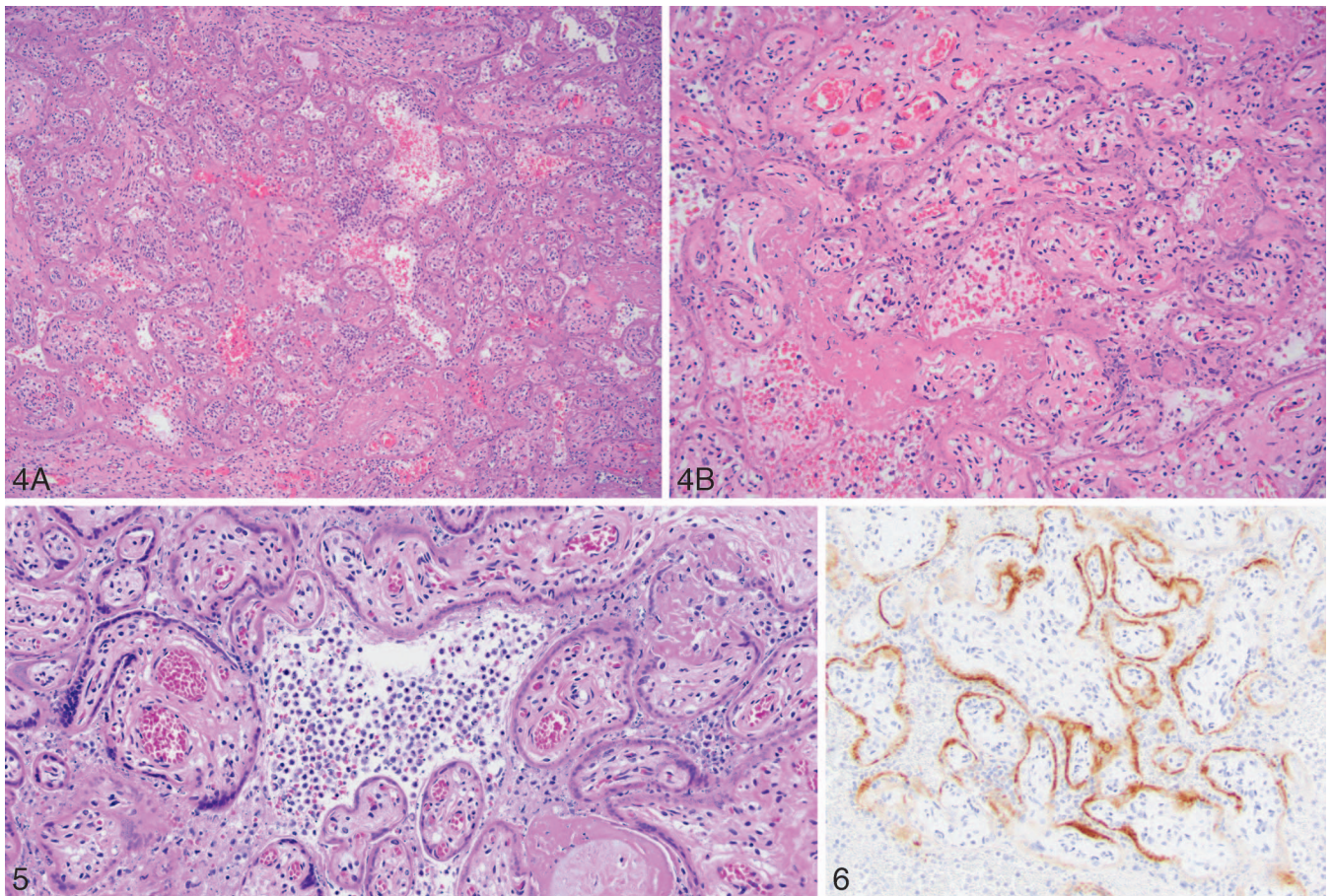


Figure 4. A and B, Placenta from a stillborn fetus demonstrating the features of SARS-CoV-2 placentitis including massive perivillous fibrin deposition, chronic histiocytic intervillitis, and syncytiotrophoblast necrosis (hematoxylin-eosin, original magnifications $\times 4$ [A] and $\times 10$ [B]).

Figure 5. An area of intervillitis 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 $\times 20$).

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 $\times 20$).

References

- Schwartz DA, Dhaliwal A. Infections in pregnancy with COVID-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: experiences with coronaviruses, parainfluenza, metapneumovirus respiratory syncytial virus, and influenza. *Arch Pathol Lab Med.* 2020;144(8):920–928. doi:10.5858/arpa.2020-0211-SA
- Schwartz DA, Graham AL. Potential maternal and infant outcomes from coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. *Viruses.* 2020;12(2):194. doi:10.3390/v12020194
- Zhang L, Jiang Y, Wei M, et al. Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province [in Chinese]. *Zhonghua Fu Chan Ke Za Zhi.* 2020;55:166–171. doi:10.3760/cma.j.cn112141-20200218-00111
- Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Arch Pathol Lab Med.* 200;144(7):799–805. doi:10.5858/arpa.2020-0901-SA
- Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020;395(10226):809–815. doi:10.1016/S0140-6736(20)30360-3
- Schwartz DA. The effects of pregnancy on women with COVID-19: maternal and infant outcomes. *Clin Infect Dis.* 2020;71(16):2042–2044. doi:10.1093/cid/ciaa559
- World Health Organization. Tracking SARS-CoV-2 variants. <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>. Updated March 29, 2022. Accessed April 2, 2022.
- Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvariants%2Fvariant-info.html. Updated December 1, 2021. Accessed January 10, 2022.
- Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(44):1641–1647. doi:10.15585/mmwr.mm6944e3
- Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: a systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand.* 2020;99(7):823–829. doi:10.1111/aogs.13867
- Kumar M, Puri M, Yadav R, et al. Stillbirths and the COVID-19 pandemic: looking beyond SARS-CoV-2 infection. *Int J Gynaecol Obstet.* 2021;153(1):76–82. doi:10.1002/ijgo.13564
- Kniffka MS, Nitsche N, Rau R, Kühn M. Stillbirths in Germany: on the rise, but no additional increases during the first COVID-19 lockdown. *Int J Gynaecol Obstet.* 2021;155(3):483–489. doi:10.1002/ijgo.13832
- Arnaez J, Ochoa-Sangrador C, Caserío S, et al. Lack of changes in preterm delivery and stillbirths during COVID-19 lockdown in a European region. *Eur J Pediatr.* 2021;180(6):1997–2002. doi:10.1007/s00431-021-03984-6
- Hedley PL, Hedermann G, Hagen CM, et al. Preterm birth, stillbirth and early neonatal mortality during the Danish COVID-19 lockdown [published online November 16, 2021]. *Eur J Pediatr.* doi:10.1007/s00431-021-04297-4
- Shah PS, Ye XY, Yang J, Campitelli MA. Preterm birth and stillbirth rates during the COVID-19 pandemic: a population-based cohort study. *CMAJ.* 2021;193(30):E1164–E1172. doi:10.1503/cmaj.210081
- Hayakawa S, Komine-Aizawa S, Mor GG. Covid-19 pandemic and pregnancy. *J Obstet Gynaecol Res.* 2020;46(10):1958–1966. doi:10.1111/jog.14384

17. King A. Doctors investigate several stillbirths among moms with COVID-19. *Scientist*. April 23, 2021. <https://www.the-scientist.com/news-opinion/doctors-investigate-several-stillbirths-among-moms-with-covid-19-68703>. Accessed Month 00, 0000.
18. Homer CSE, Leisher SH, Aggarwal N, et al. Counting stillbirths and COVID 19—there has never been a more urgent time. *Lancet Glob Health*. 2021; 9(1):e10–e11. doi:10.1016/S2214-109X(20)30456-3
19. Khalil A, von Dadelszen P, Draycott T, Ugwumadu A, O'Brien P, Magee L. Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic. *JAMA*. 2020;324(7):705–706. doi:10.1001/jama.2020.12746
20. Amaral WND, Moraes CL, Rodrigues APDS, Noll M, Arruda JT, Mendonça CR. Maternal coronavirus infections and neonates born to mothers with SARS-CoV-2: a systematic review. *Healthcare (Basel)*. 2020;8(4):511. doi:10.3390/healthcare8040511
21. Royal College of Physicians of Ireland. Covid placentitis: statement from the RCPI Faculty of Pathology and the Institute of Obstetricians and Gynaecologists. <https://www.rcpi.ie/news/releases/covid-placentitis-statement-from-the-rcpi-faculty-of-pathology-and-the-institute-of-obstetricians-and-gynaecologists/>. Published April 13, 2021. Accessed January 16, 2022.
22. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol*. 2021;225(5):522.e1–522.e11. doi:10.1016/j.ajog.2021.05.016
23. DeSisto CL, Wallace B, Simeone RM, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization—United States, March 2020–September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1640–1645. doi:10.15585/mmwr.mm7047e1
24. Neu N, Duchon J, Zachariah P. TORCH infections. *Clin Perinatol*. 2015; 42(1):77–103. doi:10.1016/j.clp.2014.11.001
25. Schwartz DA, Anoko JA, Abramowitz S. (Eds.) *Pregnant in the Time of Ebola: Women and Their Children in the 2013–2015 West African Epidemic*. New York, NY: Springer Nature; 2019.
26. Schwartz DA. The origins and emergence of Zika virus, the newest TORCH infection: what's old is new again. *Arch Pathol Lab Med*. 2017;141(1): 18–25. doi:10.5858/arpa.2016-0429-ED
27. Schwartz DA, Morotti D. Placental pathology of COVID-19 with and without fetal and neonatal infection: trophoblast necrosis and chronic histiocytic intervillositis as risk factors for transplacental transmission of SARS-CoV-2. *Viruses*. 2020;12(11):1308. doi:10.3390/v12111308
28. Watkins JC, Torous VF, Roberts DJ. Defining severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) placentitis: a report of 7 cases with confirmatory in situ hybridization, distinct histomorphologic features, and evidence of complement deposition. *Arch Pathol Lab Med*. 2021;145(11): 1341–1349. doi:10.5858/arpa.2021-0246-SA
29. Schwartz DA, Baldewijns M, Benachi A, et al. Chronic histiocytic intervillositis with trophoblast necrosis is a risk factor associated with placental infection from coronavirus disease 2019 (COVID-19) and intrauterine maternal-fetal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in live-born and stillborn infants. *Arch Pathol Lab Med*. 2021;145(5):517–528. doi:10.5858/arpa.2020-0771-SA
30. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group consensus statement. *Arch Pathol Lab Med*. 2016;140(7):698–713. doi:10.5858/arpa.2015-0225-CC
31. World Health Organization. Definition and categorization of the timing of mother-to-child transmission of SARS-CoV-2. <https://www.who.int/publications/item/WHO-2019-nCoV-mother-to-child-transmission-2021.1>. Published February 7, 2021. Accessed February 2, 2022.
32. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet*. 2016;387(10018):587–603. doi:10.1016/S0140-6736(15)00837-5
33. Nahmias AJ, Panigel M, Schwartz DA. The eight most frequent blood-borne infectious agents affecting the placenta and fetus: a synoptic review. *Placenta*. 1994;15(suppl 1):193–213.
34. Nahmias AJ, Walls KW, Stewart JA, Herrmann KL, Flynt WJ Jr. The ToRCH complex—perinatal infections associated with toxoplasma and rubella, cytomegal- and herpes simplex viruses. *Pediatr Res*. 1971;5(8):405–406.
35. Rosenberg AZ, Yu W, Hill DA, Reyes CA, Schwartz DA. Placental pathology of Zika virus: viral infection of the placenta induces villous stromal macrophage (Hofbauer cell) proliferation and hyperplasia. *Arch Pathol Lab Med*. 2017;141(1):43–48. doi:10.5858/arpa.2016-0401-OA
36. Schwartz DA. Viral infection, proliferation, and hyperplasia of Hofbauer cells and absence of inflammation characterize the placental pathology of fetuses with congenital Zika virus infection. *Arch Gynecol Obstet*. 2017;295(6):1361–1368. doi:10.1007/s00404-017-4361-5
37. Prabhu M, Cagino K, Matthews KC, et al. Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: a prospective cohort study. *BJOG*. 2020;127(12):1548–1556. doi:10.1111/1471-0528.16403
38. Chen S, Huang B, Luo DJ, et al. Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases [in Chinese]. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(5):418–423. doi:10.3760/cma.j.cn112151-20200225-00138
39. Schwartz DA, Thomas KM. Characterizing COVID-19 maternal-fetal transmission and placental infection using comprehensive molecular pathology. *EBioMedicine*. 2020;60:102983. doi:10.1016/j.ebiom.2020.102983
40. Patanè L, Morotti D, Giunta MR, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. *Am J Obstet Gynecol MFM*. 2020;2(3):100145. doi:10.1016/j.ajogmf.2020.100145
41. Kirtsman M, Diambomba Y, Poutanen SM, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. *CMAJ*. 2020;192(24):E647–E650. doi:10.1503/cmaj.200821
42. Cetta J, Bugatti M, Drera E, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. *EBioMedicine*. 2020;59:102951. doi:10.1016/j.ebiom.2020.102951
43. Sisman J, Jaleel MA, Moreno W, et al. Intrauterine transmission of SARS-CoV-2 infection in a preterm infant. *Pediatr Infect Dis J*. 2020;39(9):e265–e267. doi:10.1097/INF.0000000000002815
44. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. 2020;11(1):3572. doi:10.1038/s41467-020-17436-6
45. Hosier H, Farhadian SF, Morotti RA, et al. SARS-CoV-2 infection of the placenta. *J Clin Invest*. 2020;130(9):4947–4953. doi:10.1172/JCI139569
46. Pulinx B, Kieffer D, Michiels I, et al. Vertical transmission of SARS-CoV-2 infection and preterm birth. *Eur J Clin Microbiol Infect Dis*. 2020;39:2441–2445. doi:10.1007/s10096-020-03964-y
47. Debelenko L, Katsyv I, Chong AM, Peruyero L, Szabolcs M, Uhlemann AC. Trophoblast damage with acute and chronic intervillositis: disruption of the placental barrier by severe acute respiratory syndrome coronavirus 2. *Hum Pathol*. 2020;109:69–79. doi:10.1016/j.humpath.2020.12.004
48. Schoenmakers S, Snijder P, Verdijk RM, et al. Severe acute respiratory syndrome coronavirus 2 placental infection and inflammation leading to fetal distress and neonatal multiorgan failure in an asymptomatic woman. *J Pediatric Infect Dis Soc*. 2021;10(5):556–561. doi:10.1093/jpids/piaa153
49. Heazell AE, Worton SA, Higgins LE, et al. IFPA Gábor Than Award lecture: recognition of placental failure is key to saving babies' lives. *Placenta*. 2015; 36(suppl 1):S20–S28. doi:10.1016/j.placenta.2014.12.017
50. Man J, Hutchinson JC, Heazell AE, Ashworth M, Jeffrey I, Sebire NJ. Stillbirth and intrauterine fetal death: role of routine histopathological placental findings to determine cause of death. *Ultrasound Obstet Gynecol*. 2016;48(5): 579–584. doi:10.1002/uog.16019
51. Manktelow BN, Smith LK, Evans TA, et al. *MRRACE-UK Perinatal Mortality Surveillance Report: UK Perinatal Death for Births From January to December 2013: Supplementary Report: UK Trusts and Health Boards*. Leicester, United Kingdom: Infant Mortality and Morbidity Studies Group, Department of Health Sciences, University of Leicester; 2015.
52. Gibbins KJ, Pinar H, Reddy UM, et al. Findings in stillbirths associated with placental disease. *Am J Perinatol*. 2020;37(7):708–715. doi:10.1055/s-0039-1688472
53. Tellefsen CH, Vogt C. How important is placental examination in cases of perinatal deaths? *Pediatr Dev Pathol*. 2011;14(2):99–104. doi:10.2350/10-07-0870-OA.1
54. Graham N, Heazell AEP. When the fetus goes still and the birth is tragic: the role of the placenta in stillbirths. *Obstet Gynecol Clin North Am*. 2020;47(1): 183–196. doi:10.1016/j.ogc.2019.10.005
55. Roescher AM, Timmer A, Erwich JJ, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: a systematic review. *PLoS One*. 2014;9(2):e89419. doi:10.1371/journal.pone.0089419
56. Manocha A, Ravikumar G, Crasta J. Placenta in intrauterine fetal demise (IUFD): a comprehensive study from a tertiary care hospital. *J Matern Fetal Neonatal Med*. 2019;32(23):3939–3947. doi:10.1080/14767058.2018.1479390
57. Husen MF, van der Meeren LE, Verdijk RM, et al. Unique severe COVID-19 placental signature independent of severity of clinical maternal symptoms. *Viruses*. 2021;13(8):1670. doi:10.3390/v13081670
58. Bouachba A, Allias F, Nadaud B, et al. Placental lesions and SARS-Cov-2 infection: diffuse placenta damage associated to poor fetal outcome. *Placenta*. 2021;112:97–104. doi:10.1016/j.placenta.2021.07.288
59. Schwartz DA, Levitan D. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infecting pregnant women and the fetus, intrauterine transmission, and placental pathology during the coronavirus disease 2019 (COVID-19) pandemic: it's complicated. *Arch Pathol Lab Med*. 2021;145(8):925–928. doi:10.5858/arpa.2021-0164-ED
60. Schwartz DA, Baldewijns M, Benachi A, et al. Hofbauer cells and COVID-19 in pregnancy: molecular pathology analysis of villous macrophages, endothelial cells, and placental findings from 22 placentas infected by SARS-CoV-2 with and without fetal transmission. *Arch Pathol Lab Med*. 2021;145(11): 1328–1340. doi:10.5858/arpa.2021-0296-SA
61. Schwartz DA, Bugatti M, Santoro A, Facchetti F. Molecular pathology demonstration of SARS-CoV-2 in cytotrophoblast from placental tissue with chronic histiocytic intervillositis, trophoblast necrosis and COVID-19. *J Dev Biol*. 2021;9(3):33. doi:10.3390/jdb9030033
62. Romero R, Whitten A, Korzeniewski SJ, et al. Maternal floor infarction/massive perivillous fibrin deposition: a manifestation of maternal antifetal rejection? *Am J Reprod Immunol*. 2013;70(4):285–298. doi:10.1111/aji.12143
63. Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure. *BJOG*. 2003;110(3):292–295.

64. He M, Migliori A, Maari NS, Mehta ND. Follow-up and management of recurrent pregnancy losses due to massive perivillous fibrinoid deposition. *Obstet Med*. 2018;11(1):17–22. doi:10.1177/1753495X17710129
65. Faye-Petersen OM, Ernst LM. Maternal floor infarction and massive perivillous fibrin deposition. *Surg Pathol Clin*. 2013;6(1):101–114. doi:10.1016/j.path.2012.10.002
66. Kim EN, Lee JY, Shim JY, et al. Clinicopathological characteristics of miscarriages featuring placental massive perivillous fibrin deposition. *Placenta*. 2019;86:45–51. doi:10.1016/j.placenta.2019.07.006
67. Katzman PJ, Genest DR. Maternal floor infarction and massive perivillous fibrin deposition: histological definitions, association with intrauterine fetal growth restriction, and risk of recurrence. *Pediatr Dev Pathol*. 2002;5(2):159–164. doi:10.1007/s10024001-0195-y
68. Devisme L, Chauvière C, Franquet-Ansart H, et al. Perinatal outcome of placental massive perivillous fibrin deposition: a case-control study. *Prenat Diagn*. 2017;37(4):323–328. doi:10.1002/pd.5013
69. Lampi K, Papadogiannakis N, Sirotkina M, Pettersson K, Ajne G. Massive perivillous fibrin deposition of the placenta and pregnancy outcome: a retrospective observational study. *Placenta*. 2022;117:213–218. doi:10.1016/j.placenta.2021.12.013
70. Spinillo A, Gardella B, Muscettola G, Cesari S, Fiandrino G, Tziaila C. The impact of placental massive perivillous fibrin deposition on neonatal outcome in pregnancies complicated by fetal growth restriction. *Placenta*. 2019;87:46–52. doi:10.1016/j.placenta.2019.09.007
71. Labarrere C, Mullen E. Fibrinoid and trophoblastic necrosis with massive chronic intervillitis: an extreme variant of villitis of unknown etiology. *Am J Reprod Immunol Microbiol*. 1987;15(3):85–91. doi:10.1111/j.1600-0897.1987.tb00162.x
72. Mattuizzi A, Sauvestre F, Andre G, et al. Adverse perinatal outcomes of chronic intervillitis of unknown etiology: an observational retrospective study of 122 cases. *Sci Rep*. 2020;10(1):12611. doi:10.1038/s41598-020-69191-9
73. Jacques SM, Qureshi F. Chronic intervillitis of the placenta. *Arch Pathol Lab Med*. 1993;117(10):1032–1035.
74. Bos M, Nikkels PGJ, Cohen D, et al. Towards standardized criteria for diagnosing chronic intervillitis of unknown etiology: a systematic review. *Placenta*. 2018;61:80–88. doi:10.1016/j.placenta.2017.11.012
75. Weber MA, Nikkels PG, Hamoen K, Duvekot JJ, de Krijger RR. Co-occurrence of massive perivillous fibrin deposition and chronic intervillitis: case report. *Pediatr Dev Pathol*. 2006;9(3):234–238. doi:10.2350/06-01-0019.1
76. Ozluk E, Cotelingam J, Ong M. Massive perivillous fibrin deposition and chronic histiocytic intervillitis of a placenta: rare co-existence. *Am J Clin Pathol*. 2020;154(suppl 1):S34.
77. Abdulghani S, Moretti F, Gruslin A, Grynspan D. Recurrent massive perivillous fibrin deposition and chronic intervillitis treated with heparin and intravenous immunoglobulin: a case report. *J Obstet Gynaecol Can*. 2017;39(8):676–681. doi:10.1016/j.jogc.2017.03.089
78. Redline RW, O’Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. *Arch Pathol Lab Med*. 2000;124(12):1785–1791. doi:10.5858/2000-124-1785-PLAWCP
79. Driscoll SG. Autopsy following stillbirth: a challenge neglected. In: Ryder OA, Byrd ML, eds. *One Medicine*. Berlin, Germany: Springer-Verlag; 1984:20–31.
80. Linehan L, O’Donoghue K, Dineen S, White J, Higgins JR, Fitzgerald B. SARS-CoV-2 placentitis: an uncommon complication of maternal COVID-19. *Placenta*. 2021;104:261–266. doi:10.1016/j.placenta.2021.01.012
81. Roberts J, Cheng JD, Moore E, Ransom C, Ma M, Rogers BB. Extensive perivillous fibrin and intervillous histiocytosis in a SARS-CoV-2 infected placenta from an uninfected newborn: a case report including immunohistochemical profiling. *Pediatr Dev Pathol*. 2021;24(6):581–584. doi:10.1177/1093526621102512
82. Shook LL, Brigida S, Regan J, et al. SARS-CoV-2 placentitis associated with B.1.617.2 (delta) variant and fetal distress or demise [published online January 13, 2022]. *J Infect Dis*. doi:10.1093/infdis/jiac008
83. Hunt K, Kennedy SH, Vatish M. Definitions and reporting of placental insufficiency in biomedical journals: a review of the literature. *Eur J Obstet Gynecol Reprod Biol*. 2016;205:146–149. doi:10.1016/j.ejogrb.2016.08.029
84. Gagnon R. Placental insufficiency and its consequences. *Eur J Obstet Gynecol Reprod Biol*. 2003;110(suppl 1):S99–S107. doi:10.1016/s0301-2115(03)00179-9
85. Mazarico E, Molinet-Coll C, Martinez-Portilla RJ, Figueras F. Heparin therapy in placental insufficiency: systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2020;99(2):167–174. doi:10.1111/aogs.13730
86. Wardinger JE, Ambati S. Placental insufficiency. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021.
87. Furuya N, Hasegawa J, Doi M, Koike J, Suzuki N. Accuracy of prenatal ultrasound in evaluating placental pathology using superb microvascular imaging: a prospective observation study. *Ultrasound Med Biol*. 2022;48(1):27–34. doi:10.1016/j.ultrasmedbio.2021.09.002
88. Ohgiya Y, Nobusawa H, Seino N, et al. MR Imaging of fetuses to evaluate placental insufficiency. *Magn Reson Med Sci*. 2016;15(2):212–219. doi:10.2463/mrms.mp.2015-0051
89. Andescavage N, Kapse K, Lu YC, et al. Normative placental structure in pregnancy using quantitative magnetic resonance imaging. *Placenta*. 2021;112:172–179. doi:10.1016/j.placenta.2021.07.296
90. Aughwane R, Ingram E, Johnstone ED, Salomon LJ, David AL, Melbourne A. Placental MRI and its application to fetal intervention. *Prenat Diagn*. 2020;40(1):38–48. doi:10.1002/pd.5526
91. Fitzgerald B, O’Donoghue, McEntagart N, et al. Fetal deaths in Ireland due to SARS-CoV-2 placentitis caused by SARS-CoV-2 alpha [published online January 12, 2022]. *Arch Pathol Lab Med*. doi:10.5858/arpa.2021-0586-SA
92. di Gioia C, Zullo F, Bruno Vecchio RC, et al. Stillbirth and fetal capillary infection by SARS-CoV-2. *Am J Obstet Gynecol MFM*. 2021;4(1):100523. doi:10.1016/j.ajogmf.2021.100523
93. Dumont S, Balduyck J, Reynders M, Vanwalleghem L, Lebbe B. Acute SARS-CoV-2 alpha variant infection leading to placental insufficiency and fetal distress [published online October 7, 2021]. *J Med Virol*. doi:10.1002/jmv.27379
94. Biringer K, Sivakova J, Marcinek J, et al. Placental pathology concerning sudden foetal demise in SARS-CoV-2 positive asymptomatic pregnant female. *Bioméd Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2021;165(3):328–331. doi:10.5507/bp.2021.044
95. Lesieur E, Torrents J, Fina F, et al. Congenital infection of SARS-CoV-2 with intrauterine foetal death: a clinicopathological study with molecular analysis [published online September 23, 2021]. *Clin Infect Dis*. doi:10.1093/cid/ciab840
96. Garrido-Pontnou M, Navarro A, Camacho J, et al. Diffuse trophoblast damage is the hallmark of SARS-CoV-2-associated fetal demise. *Mod Pathol*. 2021;34(9):1704–1709. doi:10.1038/s41379-021-00827-5
97. Babal P, Krivosikova L, Sarvaicova L, et al. Intrauterine fetal demise after uncomplicated COVID-19: what can we learn from the case? *Viruses*. 2021;13(12):2545. doi:10.3390/v13122545
98. Libbrecht S, Van Cleemput J, Vandekerckhove L, et al. A rare but devastating cause of twin loss in a near-term pregnancy highlighting the features of severe SARS-CoV-2 placentitis. *Histopathology*. 2021;79(4):674–676. doi:10.1111/his.14402
99. Marton T, Hargitai B, Hunter K, Pugh M, Murray P. Massive perivillous fibrin deposition and chronic histiocytic intervillitis a complication of SARS-CoV-2 infection. *Pediatr Dev Pathol*. 2021;24(5):450–454. doi:10.1177/10935266211020723
100. Pinar H, Sung CJ, Oyer CE, Singer DB. Reference values for singleton and twin placental weights. *Pediatr Pathol Lab Med*. 1996;16(6):901–907. doi:10.1080/15513819609168713
101. Zaigham M, Gisselsson, Sand A, et al. Clinical and pathological features of SARS-CoV-2 infected placentas in pregnancies with impaired foetal outcome: a case-series of 13 placentas with and without vertical transmission. *BJOG*. 2022;117:47–56. doi:10.1016/j.placenta.2021.10.012
102. Marinho PS, da Cunha AJLA, Chimelli L, et al. Case report: SARS-CoV-2 mother-to-child transmission and fetal death associated with severe placental thromboembolism. *Front Med (Lausanne)*. 2021;8:677001. doi:10.3389/fmed.2021.677001
103. Richtmann R, Torloni MR, Oyamada Otani AR, et al. Fetal deaths in pregnancies with SARS-CoV-2 infection in Brazil: a case series. *Case Rep Womens Health*. 2020;27:e00243. doi:10.1016/j.crwh.2020.e00243
104. Bewley DJ, Lee J, Popescu O, Oviedo A. SARS-CoV-2 placental infection in an unvaccinated mother resulting in fetal demise. *Cureus*. 2021;13(12):e20833. doi:10.7759/cureus.20833