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SARS-CoV-2 placentitis, stillbirth, and maternal COVID-19 vaccination: clinical–pathologic correlations

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Introduction

Since the start of the COVID-19 pandemic in early 2020, pregnancy has been associated with an emerging number of complications and adverse clinical outcomes for the mother, fetus, and neonate. An investigation of 869,079 pregnant women seen at 499 hospitals in the United States between March 1, 2020 and February 28, 2021 found that those with SARS-CoV-2 infection were more likely to have preterm delivery, require intensive care, intubation, and mechanical ventilation, and have a fatal hospital outcome compared with uninfected pregnant women.[1] Although stillbirth was suspected of being a potential outcome of maternal infection with SARS-CoV-2, published data from the early phases of the pandemic were not definitive in demonstrating an etiologic relationship.[2] Then in April 2021, a report from Ireland described a temporal cluster of 6 stillbirths and 1 miscarriage in County Cork from pregnant

Stillbirth is a recognized complication of COVID-19 in pregnant women that has recently been demonstrated to be caused by SARS-CoV-2 infection of the placenta. Multiple global studies have found that the placental pathology present in cases of stillbirth consists of a combination of concurrent destructive findings that include increased fibrin deposition that typically reaches the level of massive perivillous fibrin deposition, chronic histiocytic intervillositis, and trophoblast necrosis. These 3 pathologic lesions, collectively termed SARS-CoV-2 placentitis, can cause severe and diffuse placental parenchymal destruction that can affect >75% of the placenta, effectively rendering it incapable of performing its function of oxygenating the fetus and leading to stillbirth and neonatal death via malperfusion and placental insufficiency. Placental infection and destruction can occur in the absence of demonstrable fetal infection. Development of SARS-CoV-2 placentitis is a complex process that may have both an infectious and immunologic basis. An important observation is that in all reported cases of SARS-CoV-2 placentitis causing stillbirth and neonatal death, the mothers were unvaccinated. SARS-CoV-2 placentitis is likely the result of an episode of SARS-CoV-2 viremia at some time during the pregnancy. This article discusses clinical and pathologic aspects of the relationship between maternal COVID-19 vaccination, SARS-CoV-2 placentitis, and perinatal death.

Key words: COVID-19 in pregnancy, COVID-19 vaccine, massive perivillous fibrin deposition, maternal-fetal tolerance, maternal vaccination, maternal viremia, perinatal death, placental insufficiency, placental malperfusion, placental pathology, SARS-CoV-2 placentitis, stillbirth, stillbirth prevention

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women with COVID-19.[3] When the placentas from these stillborn fetuses were examined by Fitzgerald et al,[4] they were found to be infected with SARS-CoV-2 and severely compromised because of fibrin deposition, intervillositis, and necrosis. A May 2021 study in England reported the analysis of a national database of 342,080 pregnant women, among whom 3527 had COVID-19, and higher rates of fetal death among those infected with SARS-CoV-2 than among uninfected mothers.[5] On November 26, 2021, the US Centers for Disease Control and Prevention (CDC) confirmed the association of SARS-CoV-2 infection with stillbirth in a population-based study of 1,249,634 delivery hospitalizations. This investigation demonstrated that pregnant women with COVID-19 had an increased risk for stillbirth compared to uninfected women; the strength of this of association was greatest during the

surge of the SARS-CoV-2 Delta (B.1.617.2) variant (pre-Delta adjusted relative risk [aRR], 1.47; 95% confidence interval [CI], 1.27–1.71; Delta period aRR, 4.04; 95% CI, 3.28–4.97).[6]

Chronic histiocytic intervillositis and increased and massive perivillous fibrin deposition in the placenta before the pandemic

Even before the COVID-19 pandemic, both chronic histiocytic intervillositis (CHIV) and increased and massive perivillous fibrin deposition (MPFD) had been observed to occur in the placentas of newborns with perinatal complications and adverse clinical outcomes.[7–13]

CHIV is a microscopic abnormality that was rarely observed in placentas before the COVID-19 pandemic, present in <1% of pregnancies. Characterized by diffuse inflammatory infiltration of the intervillous space which consists predominantly of mononuclear inflammatory cells termed
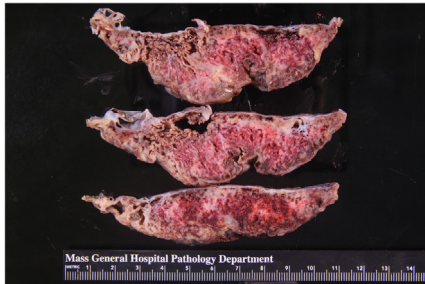
Massive perivillous fibrin deposition involves most of the placental parenchyma.

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histiocytes, Labarre and Mullen were the first to identify it as a discrete abnormality in 1987 and termed it massive chronic intervillositis.[14] Describing the intervillous infiltration of mononuclear cells in the placenta accompanied by fibrin deposits and trophoblast necrosis,[14] they hypothesized that it could represent an extreme variant of villitis of unknown etiology (VUE). Since then, the lesion has been termed in the literature variously as "intervillitis," "chronic histiocytic intervillositis of unknown etiology," "chronic

Microscopic image. Fibrin has completely obstructed the intervillous space, and there is severe ischemic necrosis of the chorionic villi. Hematoxylin and eosin staining, ×10.

MPFD, massive perivillous fibrin deposition.

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intervillositis," "massive chronic intervillositis," "chronic histiocytic intervillositis," "chronic intervillositis of unknown etiology," "massive perivillous histiocytosis," and "massive histiocytic chronic intervillositis."[15,16] CHIV is frequently accompanied by increased fibrin deposition,[7–13,17] which in some cases can be severe enough to constitute MPFD. CHIV can resemble processes observed in infections such as the chronic stage of placental malaria, where accumulations of histiocytes in the intervillous space can develop.[18] Although malaria is endemic in some regions affected by COVID-19,[19] placentas affected by malaria will also typically demonstrate *Plasmodium*–parasitized red blood cells and hemozoin pigment in the intervillous space, without prominent fibrin deposition or trophoblast necrosis. It was recognized long before COVID-19 that intervillositis is a potentially serious placental abnormality, not only causing intrauterine growth restriction, miscarriage, and stillbirth, but also having a substantial risk of recurrence.[7–13,17] Cases of CHIV were also described occurring with chronic villitis, a microscopic abnormality in which the chorionic villi are infiltrated by lymphocytes, plasma cells, and/or histiocytes, and which can result from TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes) infections.[16] A recent hypothesis has suggested that CHIV could be linked with anti–human leukocyte antigen alloimmunization, as could be observed in graft rejection.[20]

Similar to intervillositis, MPFD was recognized long before the COVID-19 pandemic as a cause of perinatal morbidity and mortality owing to fetal hypoxic injury that results in spontaneous abortion, intrauterine growth restriction, preterm delivery, stillbirth, neonatal death, and neurologic disease in surviving infants, along with its substantial risk for recurrence.[21–23] The characteristic features of MPFD include extensive and confluent deposition of fibrin/fibrinoid material within the intervillous space that obstructs maternal perfusion and gas–nutrient exchange, encases the chorionic villi, and causes villous ischemia and necrosis

that eventually result in placental insufficiency.[21–23] Even before the current COVID-19 pandemic, MPFD has been reported in autopsied infants whose cause of death was placental insufficiency. Although MPFD is technically not an inflammatory disorder, it has commonly occurred together with chronic inflammatory conditions including CHIV and villitis.

SARS-CoV-2 placentitis and the importance of pathology in understanding the mechanisms of stillbirth from COVID-19

The role of pathology in revealing substantial information on the effects of SARS-CoV-2 on the placenta and the mechanisms of fetal demise has reinforced the advantages of submitting for examination placentas from infected mothers with adverse perinatal outcomes. Multiple studies of placentas infected with SARS-CoV-2 have identified a grouping of unusual pathologic abnormalities that can be present in both live-born and stillborn infants.[24–30] These findings include increased perivillous fibrin deposition that, in most cases, reaches the extent of MPFD (Figures 1 and 2); trophoblast necrosis (Figure 2); and CHIV (Figures 2 and 3). Both MPFD and CHIV were rarely observed in placentas before the COVID-19 pandemic. The simultaneous finding of these 3 abnormalities in infected placentas from mothers with COVID-19 has been termed "SARS-CoV-2 placentitis" by Watkins et al.[29] Syncytiotrophoblast is the most common placental cell type to be infected with SARS-CoV-2 (Figure 4),[2] although the virus has now been identified in all cells of the chorionic villi. To determine the cause of perinatal deaths occurring in pregnant women with COVID-19, Schwartz et al[31] examined a cohort of placentas infected with SARS-CoV-2 from 64 stillborn fetuses and 4 early neonatal deaths from 12 countries. Findings from this investigation demonstrated that all 68 placentas had severe destructive pathology from the constituents of SARS-CoV-2 placentitis, and that there was coexistent CHIV, increased fibrin deposition, and
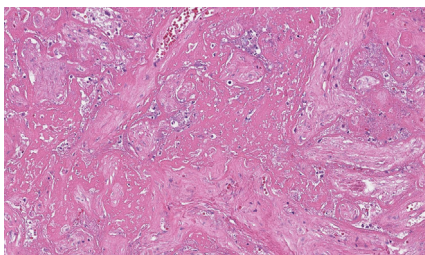
trophoblast necrosis in 97% of placentas. A striking finding was that the average infected placenta had 77.7% tissue destruction resulting from widespread involvement with SARS-CoV-2 placentitis, with many placentas having >90% of the parenchyma destroyed. This extent of placental destruction substantially impedes delivery of adequate oxygen and nutrients to the fetus and is incompatible with fetal survival. Another important finding in this study was that although SARS-CoV-2 was identified in perinatal body specimens in 16 of 28 (57%) cases tested, and autopsies were performed on 29 stillborn fetuses and 1 neonate, there was no evidence that perinatal mortality was induced by direct viral infection of fetal organs. Instead, the tissue damage seemed to be confined to the placenta, where it was extensive and highly destructive in all 68 cases. The authors concluded that placental insufficiency from SARS-CoV-2 placentitis and consequent severe fetal hypoxia produced a hypoxic-ischemic fetal or neonatal demise. This mechanism of fetal death is not typical of intrauterine infections, which typically result in stillbirth from direct damage to the fetal somatic organs. Similar results to these by Schwartz et al[31] were found in subsequent investigations of stillbirth. In Sweden, Zaigham et al[32] reported 5 stillborn fetuses from mothers having COVID-19 in which all placentas were infected with SARS-CoV-2 and had concomitant SARS-CoV-2 placentitis. A report from Greece by Konstantinidou et al[33] described 6 stillborn fetuses from mothers having SARS-CoV-2 infection during pregnancy, with placentas afflicted with SARS-CoV-2 placentitis. Two of the mothers were asymptomatic and 4 had only mild symptoms, with stillbirth occurring from 3 to 15 days after the initial maternal COVID-19 diagnosis. In all 6 placentas there was MPFD that involved between 75% and 90% of the parenchyma. None of the 6 fetuses were found to be infected with SARS-CoV-2, and all 3 of the autopsies performed showed evidence of asphyxia. A common factor among the reports of SARS-CoV-2 placentitis causing perinatal deaths,

including those from Schwartz et al,[31] Zaigham et al,[32] Konstantinidou et al,[33] and Fitzgerald et al,[4] was that in all cases the mothers were unvaccinated against COVID-19.
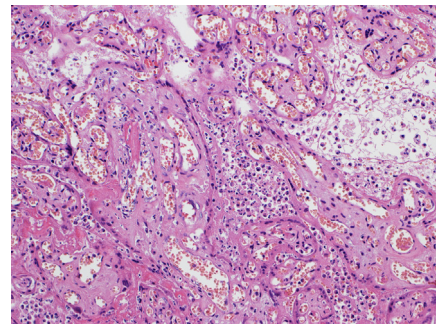
These studies and others indicate that one mechanism of fetal and neonatal mortality from maternal COVID-19 involves the development of placental infection causing SARS-CoV-2 placentitis and placental insufficiency.[2] As SARS-CoV-2 infection of the placenta evolves, increasingly severe parenchymal ischemia occurs, in which fibrin deposition and/or MPFD, trophoblast necrosis, and CHIV obstruct maternal perfusion in the intervillous space, leading to progressive destruction of the tissue and malperfusion. SARS-CoV-2 placentitis is often accompanied by other placental abnormalities that contribute to malperfusion; these include thrombohematomas, villitis, and findings of maternal and fetal vascular malperfusion.[30–32,34] The resulting placental insufficiency in severe cases causes hypoxemic ischemic injury to the vital organs of the fetus, resulting in intrauterine fetal death or neonatal demise.[2,31] An interesting and as yet unexplained observation from these reported cases is that there seems to be little correlation between the severity of maternal disease, placental infection, and stillbirth. In fact, some cases of SARS-CoV-2 placentitis and stillbirth occur in asymptomatic women, a dichotomy which has yet to be understood.

SARS-CoV-2 placentitis and SARS-CoV-2 viremia

Placentas having SARS-CoV-2 placentitis generally demonstrate unusually intense and diffuse positivity for viral antigens and nucleic acids according to immunohistochemistry and nucleic acid hybridization methods when compared with other viral infections.[4,24–30] It has been assumed that SARS-CoV-2 reaches the placenta via the maternal bloodstream, a process termed "hematogenous transmission," which is characteristic of not only viral but also many bacterial and parasitic agents that can cause intrauterine infection.[35,36] As a result of maternal viremia, TORCH

agents including viruses such as Ebola virus, Lassa virus, parvovirus B19, Zika virus, and others can reach the maternal-
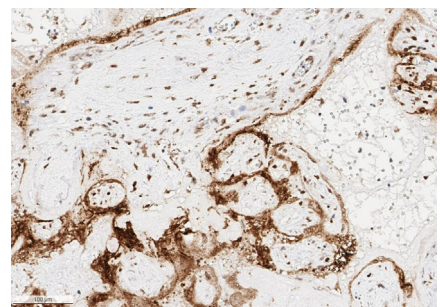
Proposed mechanisms of development of placental infection and SARS-CoV-2 placentitis
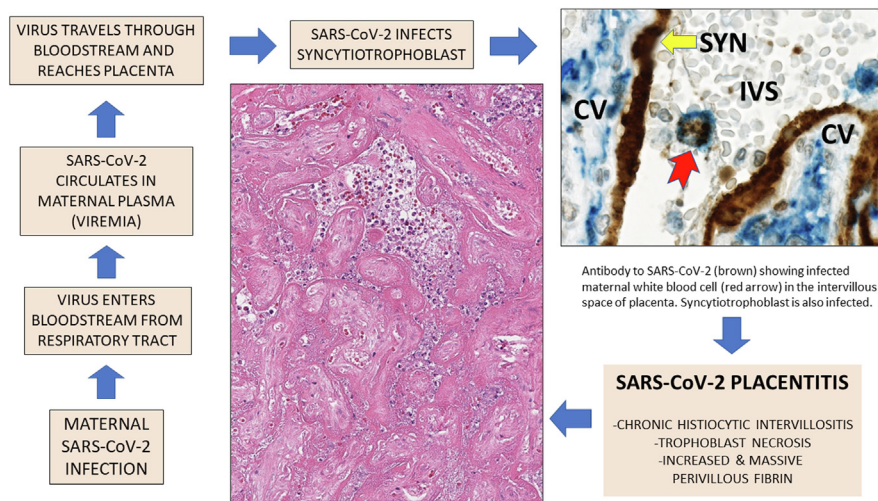
Proposed mechanisms of placental infection with SARS-CoV-2 following maternal viremia and development of SARS-CoV-2 placentitis. The high magnification photograph of placenta in the upper right demonstrates a maternal white blood cell, probably a macrophage, staining for SARS-CoV-2 using immunohistochemistry and circulating in the intervillous space, adjacent to the infected syncytiotrophoblast.

CV, chorionic villus; *IVS*, intervillous space; *SYN*, syncytiotrophoblast.

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fetal interface to infect the placenta and, in many cases, the fetus.[37] SARS-CoV-2 is the newest TORCH virus,[38] and although there are currently no data to confirm this, it is highly probable that it reaches the placenta via the hematogenous route following an episode(s) of maternal viremia as occurs with other TORCH viruses (Figure 5).[2,25,31]

The precise mechanisms involved in the development of SARS-CoV-2 placentitis are not well understood. However, it is generally believed that placental disease is initiated by SARS-CoV-2 infection of the syncytiotrophoblast and cytotrophoblast, triggering complement activation and subsequent cytokine upregulation recruiting maternal monocytes to the area of infection. Syncytiotrophoblast necrosis occurs, which is not only the result of direct viral infection but also partially owing to complement activation and irreversible damage to the microvillous apical border of these cells, and which eventually involves the cytotrophoblast. Cytokines in the area of tissue damage result in a procoagulant microenvironment, eliciting fibrin deposition that typically reaches the level of MPFD, and SARS-CoV-2 placentitis.[29,39,40] Necrosis of the infected trophoblast, the primary protective cell layer of the maternal-fetal interface, may in some cases permit viral entry into the villous stroma and chorionic vasculature. Supporting this is the pathology demonstration of SARS-CoV-2 in not only syncytiotrophoblast but also in cytotrophoblast, villous stromal and Hofbauer cells, and villous capillary endothelium.[30,41,42]

Similar to other respiratory viruses such as influenza viruses, SARS-CoV-1, adenoviruses, and respiratory syncytial virus, SARS-CoV-2 can be detected in the human bloodstream, which is a finding that has been termed both "viremia" and "RNAemia."[43–45] SARS-CoV-2 viremia and systemic dissemination, as demonstrated by levels of plasma RNAemia, are associated with increased severity of tissue damage, endothelial inflammation, elevation in levels of inflammatory biomarkers, a hyperinflammatory state, and coagulopathies, and can predict the risk of eventual disease severity and death.[46–52] Further support for bloodstream dissemination of SARS-CoV-2 to extrapulmonary organs has been provided by autopsy studies that have identified the virus in multiple tissues including lymphatic, cardiovascular, gastrointestinal, endocrine, reproductive organ, liver, bone marrow, urinary tract, and of course placental tissue, where it can be associated with organ malfunction and pathology.[1,43–45] SARS-CoV-2 viremia is associated with complement system activation and elevated proinflammatory cytokine levels, which may explain many of the destructive effects that occur in extrapulmonary organs including the placenta.[29,43,45,47,53] Both the development and effects of SARS-CoV-2 viremia are likely dependent on multiple factors such as genetics, immunocompetence, comorbidities, history of COVID-19 infection, vaccination status, viral factors, and other covariables. In nonpregnant adults, the detection of SARS-CoV-2 viremia/RNAemia is associated with worse disease outcomes, including increased probability of progression to severe disease, higher levels of interleukin (IL)-6, IL-5, or C-X-C motif chemokine ligand (CXCL) 10, acute respiratory distress syndrome, intensive care unit (ICU) admission, critical disease, and death in hospitalized patients.[43,54–56] A proteomic study by Li et al[47] demonstrated that SARS-CoV-2 viremia was not only associated with severe disease and death, but also with up-regulation of SARS-CoV-2 cell entry factors, increased levels of markers of damage to the lungs, gastrointestinal tract, endothelium, and blood vessels, and alterations in coagulation pathways that were predictive of clinical outcomes.

The identification of SARS-CoV-2 plasma viremia can be affected by factors that include symptom duration, disease severity, and test sensitivity.[43] The incidence of viremia among

nonpregnant persons with COVID-19 varies between studies, with reported figures of 2% among infected outpatients, 6% among persons presenting to the emergency department, 47% among hospitalized patients, and up to 100% among patients in the ICU.[53,57]

Data on the incidence of SARS-CoV-2 viremia and RNAemia in pregnant women with COVID-19 are scant, and suggest that the occurrence of the virus in the bloodstream during pregnancy is an unusual or transient event that is difficult to capture in this population.[58] Edlow et al[59] found that among 65 pregnant women with SARS-CoV-2 infection, including 23 who were asymptomatic and 22 with mild, 7 with moderate, 10 with severe, and 3 with critical COVID-19 disease, there was no detectable viremia, placental infection, or vertical transmission. In contrast, in a cohort of 109 pregnant women with symptomatic COVID-19 requiring hospitalization, Maeda et al[60] found that 16 (14.7%) had SARS-CoV-2 viremia. In this cohort, maternal viremia was associated with the presence of SARS-CoV-2 in the cerebrospinal fluid and/or umbilical cord blood. There have been several cases in which viremia was identified in pregnant women having COVID-19 who subsequently had placentas with SARS-CoV-2 placentitis, and which were associated with fetal distress and stillbirth.[61,62] In one study, 6 pregnant women in Chicago had COVID-19 and SARS-CoV-2 placentitis; 1 mother was asymptomatic, 4 had mild symptoms, and 1 had moderate SARS-CoV-2 infection.[62] Two of the 6 women had low-level SARS-CoV-2 viremia detected—one was asymptomatic but had a stillbirth, and the other had mild illness and delivered an asymptomatic infant. Although information regarding the frequency of viremia in pregnancy is incomplete, what is known thus far suggests that SARS-CoV-2 in maternal blood is an unusual occurrence. If true, this can help to explain the very low incidence of SARS-CoV-2 infection of the placenta, which in one study was estimated by meta-analysis to be 7% among pregnant women having COVID-19.[63,64]

Strengthening the association between SARS-CoV-2 viremia, placental infection, and SARS-CoV-2 placentitis is the pathology observation of maternal white blood cells staining positively for SARS-CoV-2 circulating in the intervillous space of infected placentas with SARS-CoV-2 placentitis (Figure 5). Facchetti et al[25] observed multiple maternal CD14-positive macrophages/monocytes in the intervillous space that stained positive for SARS-CoV-2 RNA using an S-antisense probe and in situ hybridization in the placenta from a stillborn infant having SARS-CoV-2 placentitis. Among a cohort of 58 placentas with SARS-CoV-2 placentitis from stillbirths caused by COVID-19 and placental insufficiency, Schwartz et al[31] identified 3 placentas (5%) having macrophages in the intervillous space that were positive for SARS-CoV-2.

Pathophysiology of SARS-CoV-2 placentitis
The development of SARS-CoV-2 placentitis may be more complex than simply viral infection of placental cells. The occurrence of SARS-CoV-2 placental infection with certain chronic inflammatory lesions provides a potential pathophysiological mechanism for the immunologic basis of this destructive process. Chronic placental inflammatory lesions are a diverse group of abnormalities that are characterized by lymphocytic, plasmacellular, or histiocytic infiltration in specific anatomic compartments of the placenta that have been associated with infectious agents and immunologic disorders. In addition to its role as a respiratory, excretory, endocrine, and nutritive organ, the placenta also has complex immune functions that include maintenance of maternal-fetal tolerance. Because both the placenta and fetus are semiallografts that express paternal-derived antigens, immunologic tolerance is a requirement for a successful reproductive outcome. There is accumulating evidence that failure of maternal−fetal tolerance results in rejection of fetal-derived tissues such as the placenta, analogous to the rejection syndromes observed in allogeneic solid-organ transplantation.[65−68]

This pathologic process has been implicated in obstetrical conditions including fetal demise, preterm premature rupture of membranes, preterm labor, and recurrent pregnancy loss, and in chronic placental conditions such as MPFD and inflammatory lesions including chronic chorioamnionitis, VUE, and chronic deciduitis.[65,69−72] Chronic placental inflammation has been shown to be characterized by infiltration of fetal-derived tissues with maternal CD8$^+$ T lymphocytes, overexpression of the T lymphocyte cytokines CXCL9, CXCL10, and CXCL11 in chorionic villous stromal, endothelial, and Hofbauer cells, and C4d deposition—processes similar to those occurring in solid-organ rejection.[65,73] SARS-CoV-2 placental infection is characterized by the occurrence of multiple chronic lesions that have been proposed to result from maternal antifetal rejection. Under these circumstances, fetal demise owing to placentitis and placental insufficiency would represent an extreme form of rejection.[65,69]

Further supporting the immunologic basis underlying SARS-CoV-2 placentitis is the occurrence of pathology abnormalities frequently present in placentas infected with SARS-CoV-2—CHIV, VUE, and MPFD—in diseases associated with immune alterations including systemic lupus erythematosus, autoimmune thyroid disease, and Sjögren's syndrome.[74]

Clinical evidence for maternal COVID-19 vaccination preventing stillbirth
The US Food and Drug Administration granted initial emergency use authorization for the Pfizer−BioNTech messenger RNA (mRNA) vaccine on December 11, 2020 and for the Moderna mRNA vaccine on December 18, 2020, after which mass vaccinations were initiated immediately throughout the United States and other high-income countries. However, as is often the case, pregnant women remained an undervaccinated group. There were many reasons—pregnant women were excluded from the initial vaccine trials, there was limited experience with mRNA vaccines in this group,

suboptimal communication and guidance were provided by official sources and professional agencies, and there was widespread antivaccine disinformation distributed via social media and news outlets, resulting in vaccine hesitancy.[75–77] By May 2021, only 16% of pregnant women in the United States received at least 1 dose of a COVID-19 vaccine.[78] The problem was compounded by the spread of the SARS-CoV-2 Delta variant in 2021, which caused an increase in disease severity among pregnant women, with almost 20% of the most critically ill hospitalized COVID-19 patients in England being unvaccinated pregnant women. The CDC responded by urgently recommending that pregnant women be vaccinated.[79]

Multiple studies have confirmed that mRNA vaccines for COVID-19 are both safe and effective when given during pregnancy,[80–82] and are highly effective in reducing maternal morbidity and mortality from SARS-CoV-2 infection.[1,58,83] The vaccines do not cause placental pathology abnormalities such as intervillositis, trophoblast necrosis, increased fibrin or MPFD, villitis and thrombohematomas that are present with SARS-CoV-2 placentitis and result in placental insufficiency[84] Importantly, maternal vaccination protects the fetus and newborn. Maternal vaccination stimulates systemic and mucosal immunity to reduce viral cell entry and reduces the incidence of SARS-CoV-2 infection. The efficacy of vaccinating pregnant women to reduce the rate of infection and prevent maternal and neonatal complications has been previously shown for influenza, another epidemic infectious disease caused by respiratory RNA viruses.[85]

COVID-19 vaccination during pregnancy induces maternal antibodies that are not only detectable in maternal sera at delivery and in breast milk, but are also present in infant sera, indicating transfer of maternal antibodies before delivery.[86,87] Administration of mRNA SARS-CoV-2 vaccines to pregnant women induces functional antispike immunoglobulin G antibodies in the maternal circulation, which pass through the placenta and can be identified in the umbilical cord blood after birth, providing protection against COVID-19 to infants.[81,88,89] The CDC found that infants born to mothers who received 2 doses of either the Pfizer or Moderna vaccines while pregnant had a 61% lower risk of being hospitalized because of COVID-19 infection in their first 6 months of age.[90]

Recently published clinical studies have confirmed the benefit of maternal vaccination for fetal and infant outcomes, including reduction of stillbirth. An investigation from a national cohort in Scotland that tracked pregnancies during the COVID-19 pandemic compared the clinical outcomes of 2364 infants delivered to vaccinated and unvaccinated mothers during the period between December 1, 2020 and October 31, 2021.[91] A total of 11 stillborn and 8 liveborn infants who died in the neonatal period were reported in this study; all deaths occurred in offspring of women who had not received COVID-19 vaccination. By the end of this study in October 2021, the vaccination coverage remained substantially lower among pregnant women compared with the nonpregnant childbearing-age female population, with 32.3% of women giving birth in October 2021 having received 2 vaccine doses vs 77.4% of all women. A systematic review and meta-analysis of the effects of maternal COVID-19 vaccination on perinatal outcomes based on 23 studies was released on May 10, 2022.[75] When 66,067 pregnant women who were vaccinated against SARS-CoV-2 while pregnant were compared with 424,624 unvaccinated pregnant women, it was found that COVID-19 vaccination was associated with a 15% reduction in stillbirths. Following this report, the results of maternal vaccination against SARS-CoV-2 from the multicenter Swiss COVI-PREG registry were reported on May 29, 2022.[92] Among 1012 women in Switzerland who received at least 1 dose of mRNA vaccine between March 1 and December 27, 2021, there was no increase in adverse pregnancy or neonatal outcomes compared with historic data on background risks, and importantly, there were no stillbirths reported. On June 1, 2022, the results of the Norwegian nationwide registry-based cohort study examining the effect of maternal vaccination on infant infection status were released. The study demonstrated that infants whose mothers had received the mRNA vaccine while pregnant had a substantially lower risk of testing positive for SARS-CoV-2 during the first 4 months of life compared with infants of mothers unvaccinated during pregnancy.[93] This reduction in the postnatal infection risk was noted during the period dominated by the Delta and Omicron variants, although the significance was greater during the Delta predominance.

An important multicenter cohort study by Hui et al[94] has provided evidence that maternal vaccination against SARS-CoV-2 results in a decreased risk of stillbirth when compared with unvaccinated women. One of the goals of this retrospective investigation from 12 maternity hospitals in Melbourne, Australia was to determine the clinical perinatal outcomes of 17,365 women who received $\geq$1 doses of the mRNA COVID-19 vaccine before or during pregnancy compared with 15,171 unvaccinated pregnant women during the period from July 1, 2021 to March 31, 2022. The vaccinated women had a substantially lower rate of stillbirth compared with the unvaccinated cohort (0.2% vs 0.8%; adjusted odds ratio, 0.18; 95% CI, 0.09–0.37; $P<.001$). Following stratification for gestational age, this association was statistically substantial only for preterm stillbirths.

On the basis of currently available data, we postulate that there is a relationship between maternal vaccination for COVID-19, SARS-CoV-2 placentitis, and stillbirth. For a virus to reach the placenta, it generally travels through the maternal bloodstream; there is no evidence that COVID-19 is a typical ascending infection that arises from the lower genital tract. In explaining the etiology of SARS-CoV-2 placentitis among 3 stillborn fetuses, Shook et al[61] suggested that maternal viremia could overcome placental immune defenses at the level of the syncytiotrophoblast. Vaccination against COVID-19 not only lowers viral load and limits viremia, but

also decreases vascular and tissue damage, reduces viral dissemination from the lungs to other organs, decreases the incidence of severe disease and death, and suppresses transmission.[95–98] These effects of COVID-19 vaccination during pregnancy can help explain the epidemiologic, clinical, and pathologic studies that indicate reduction of stillbirths among vaccinated women. However, a definitive analysis of this issue has several challenges. Placental examination was not a component of the epidemiologic clinical investigations demonstrating that vaccination provides protection to the fetus and neonate from SARS-CoV-2 infection and stillbirth. In addition, there are confounding factors to be considered, including the specific type and prevalence of the SARS-CoV-2 variants involved and the possibility that some patients may have been infected by several variants. However, correlating the clinical and epidemiologic data with those from studies of placental pathology suggests that one potential and even likely mechanism of fetal protection could be from maternal vaccination impeding maternal viremia, development of placental infection, and SARS-CoV-2 placentitis.[2] It seems beyond coincidence that in the multiple reports of SARS-CoV-2 placentitis associated with stillbirths and neonatal deaths, none of the mothers had received COVID-19 vaccinations. In addition, although not constituting proof, the authors are not aware either personally, via collegial networks, or in the published literature of any cases of SARS-CoV-2 placentitis causing stillbirths among pregnant women who received the COVID-19 vaccine. In contrast to many other TORCH agents, a 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 following transplacental transmission.[2,31] Because the tissue pathology related to COVID-19 seems to be most prominent in the placenta, where it is highly destructive, it may be possible that effective vaccination of pregnant women can either decrease the severity or even inhibit the

development of SARS-CoV-2 placentitis. Thus, maternal vaccination against COVID-19 may be life-saving for the fetus and the mother. ∎

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