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SARS-CoV-2 Placentitis, Stillbirth and Maternal COVID-19 Vaccination: Clinical-Pathological Correlations

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CONDENSATION

SARS-CoV-2 placentitis has been a cause of placental destruction and stillbirth in women who are not vaccinated for COVID-19

SHORT TITLE

Placentitis, stillbirth and maternal COVID-19 vaccination

ABSTRACT

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 findings present in cases of stillbirth consists of a combination of concurrent destructive findings that include increased fibrin deposition which typically reaches the level of massive perivillous fibrin deposition, chronic histiocytic intervillositis and trophoblast necrosis. These three pathological lesions, collectively termed SARS-CoV-2 placentitis, can cause severe and diffuse placental parenchymal destruction that can affect greater than 75% of the placenta, effectively rendering the placenta 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 immunological 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 pathological aspects of the relationship between maternal COVID-19 vaccination, SARS-CoV-2 placentitis and perinatal death.

KEYWORDS

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

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 both 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 than were uninfected pregnant women.[1] Although stillbirth was suspected of being a potential outcome of maternal infection from SARS-CoV-2, published data from the early phases of the pandemic were not definitive in demonstrating an etiological relationship.[2] Then in April 2021, a report from Ireland described a temporal cluster of six stillbirths and one miscarriage in County Cork from pregnant women with COVID-19.[3] When the placentas from these stillborn fetuses were examined by Fitzgerald et al., they were found to be infected with SARS-CoV-2 and were severely compromised due to fibrin deposition, intervillositis and necrosis.[4] A May 2021 study in England reported the analysis of a national database of 342,080 pregnant women, among whom 3,527 had COVID-19 and that there were higher rates of fetal death in those infected with SARS-CoV-2 compared to uninfected mothers.[5] On November 26, 2021, the United States 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 aRR = 1.47; 95% CI = 1.27–1.71; Delta periods aRR = 4.04; 95% CI = 3.28–4.97).[6]

Chronic Histiocytic Intervillositis, Increased and Massive Perivillous Fibrin Deposition in the Placenta Prior to the Pandemic

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

Chronic histiocytic intervillositis (CHIV) is a microscopic abnormality that was rarely seen in placentas prior to the COVID-19 pandemic, present in less than 1% of pregnancies. Characterized by diffuse inflammatory infiltration of the intervillous space which consists predominantly of mononuclear inflammatory cells termed 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 "intervillitis", "chronic histiocytic intervillositis of unknown etiology", "chronic 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 so severe as to constitute massive perivillous fibrin deposition (MPFD). CHIV can resemble processes seen 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 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, fibrin deposition is not prominent and trophoblast necrosis does not occur. It was recognized long before COVID-19 that intervillositis was a potentially serious placental abnormality – it not only caused intrauterine growth restriction, miscarriage and stillbirth, but had a significant recurrence risk.[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

infection with such TORCH (Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes) infections.[16] A hypothesis has recently put forward is that CHIV could be linked with anti-HLA alloimmunization, as could be observed in graft rejection.[20]

Similar to intervillositis, MPFD had been recognized long before the COVID-19 pandemic as a cause of perinatal morbidity and mortality due to fetal hypoxic injury that results in spontaneous abortion, intrauterine growth restriction, preterm delivery, stillbirth, neonatal death, neurologic disease in surviving infants, and it has a significant 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 results in placental insufficiency.[21-23] Even prior to the current pandemic of SARS-CoV-2 infections, MPFD had been reported from autopsied babies where the 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 significant information on the effects of SARS-CoV-2 on the placenta and the mechanisms of fetal demise has reinforced the advantages of submitting placentas for examination from infected mothers with adverse perinatal outcomes. Multiple studies of placentas infected with SARS-CoV-2 have identified a grouping of unusual pathological abnormalities that can be present in both liveborn and stillborn babies.[24-30] These findings include increased perivillous fibrin deposition that, in most cases, reaches the extent of MPFD (Figures 1, 2); trophoblast necrosis (Figure 2); and CHIV (Figures 2, 3). Both MPFD and CHIV were rarely seen in placentas prior to the COVID-19 pandemic. The simultaneous finding of these three abnormalities in infected placentas from mothers

with COVID-19 has been termed SARS-CoV-2 placentitis by Watkins and colleagues.[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. In order to determine the cause of perinatal deaths occurring in pregnant women with COVID-19, Schwartz and colleagues examined a cohort of placentas infected with SARS-CoV-2 from 64 stillborn fetuses and 4 early neonatal deaths from 12 countries.[31] Their 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 over 90% of the parenchyma destroyed. This extent of placental destruction significantly 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 a perinatal body specimen in 16 out 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 appeared 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. were found in subsequent investigations of stillbirth. In Sweden, Zaigham and colleagues reported five stillborn fetuses from mothers having COVID-19 in which all placentas were infected with SARS-CoV-2 and had concomitant SARS-CoV-2 placentitis.[32] A report from Greece by Konstantinidou et al. described 6 stillborn fetuses from mothers having SARS-CoV-2 infection during pregnancy that were associated with placentas having SARS-CoV-2 placentitis.[33]

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 for COVID-19.

These studies and others indicate that one mechanism of fetal and neonatal mortality from maternal COVID-19 is through 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 appears 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 using 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 that 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, Zika virus and other can reach the maternal-fetal interface to infect the placenta and, in many cases, the fetus.[37] SARS-CoV-2 is the newest TORCH virus,[38] and although data does not current exist 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 due to complement activation and irreversible damage to the microvillous apical border of these cells, and which eventually involve the cytotrophoblast. Cytokines in the area of tissue damage result in a procoagulant microenvironment, eliciting fibrin deposition which 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 viral infections such as influenza, SARS-CoV-1, adenovirus, and respiratory syncytial virus, SARS-CoV-2 can be detected in the human bloodstream, 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, is 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 are from autopsy studies that have identified the virus in multiple tissues including lymphatic, cardiovascular, gastrointestinal, endocrine, reproductive organs, liver, bone marrow, urinary tract, and of course, placenta, 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 that include such factors as genetics and immunocompetency, co-morbidities, previous history of COVID-19 infection, vaccination status, viral factors, as well as other co-variables. In non-pregnant 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 IL-6, IL-5 or CXCL10, 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. demonstrated that SARS-CoV-2 viremia was not only associated with severe disease and death, but also with upregulation 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.[47]

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 non-pregnant persons with COVID-19 varies between studies, with figures reported of 2% among infected outpatients, 6% of persons presenting to the emergency department, 47% of hospitalized patients and up to 100% of 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. 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 having critical COVID-19 disease, there was no detectable viremia, placental infection or vertical transmission.[59] In contrast, in a cohort of 109 pregnant women with symptomatic COVID-19 requiring hospitalization, Maeda et al. found that 16 (14.7%) had SARS-CoV-2 viremia.[60] 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; one mother was asymptomatic, 4 had mild symptoms and one 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 baby. 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. observed multiple maternal CD-14 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 having SARS-CoV-2 placentitis.[25] Among a cohort of 58 infected placentas with SARS-CoV-2 placentitis from stillbirths caused by COVID-19 and placental insufficiency, Schwartz et al. identified 3 placentas (5%) having macrophages in the intervillous space that were positive for SARS-CoV-2.[31]

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 immunological 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 as well as immunological disorders. In addition to the role of the placenta as a respiratory, excretory, endocrine, and nutritive organ, it also has complex immune functions that include maintenance of maternal-fetal tolerance. Because both the placenta and fetus are semi-allografts that express paternal-derived antigens, immunological 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 seen in allogeneic solid organ transplantation.[65-68] This pathological process has been implicated in obstetrical conditions including fetal demise, preterm premature rupture of membranes, preterm labor, and recurrent pregnancy loss, as well as in such chronic placental conditions as MPFD and inflammatory lesions including chronic chorioamnionitis, villitis of unknown etiology 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, CXCL11 in chorionic villous stromal, endothelial and Hofbauer cells, and C4d deposition – processes similar to those

284 occurring in solid organ rejection.[65,73] SARS-CoV-2 placental infection is characterized by the occurrence
285 of multiple chronic lesions that have been proposed to result from maternal anti-fetal rejection. Under
286 these circumstances, fetal demise due to placentitis and placental insufficiency would represent an
287 extreme form of rejection.[65,69]

288 Further supporting the immunological basis underlying SARS-CoV-2 placentitis is the occurrence
289 of pathology abnormalities frequently present in placentas infected with SARS-CoV-2 – CHIV, villitis of
290 unknown etiology and MPFD – in diseases associated with immune alterations including systemic lupus
291 erythematosus, autoimmune thyroid disease and Sjögrens syndrome.[74]

292 **Clinical Evidence for Maternal COVID-19 Vaccination Preventing Stillbirth**

293 The U.S Food & Drug Administration granted initial emergency use authorization for the Pfizer–
294 BioNTech mRNA vaccine on December 11th and for the Moderna mRNA vaccine on December 18th, 2020,
295 after which mass vaccinations were initiated immediately throughout the United States and other high
296 income countries. However, as is often the case, pregnant women remained an under-vaccinated group.
297 There were many reasons – pregnant women were excluded from the initial vaccine trials, there was
298 limited experience with mRNA vaccines in this group, suboptimal communications and guidance was
299 provided from official sources and professional agencies, and there was widespread antivaccine
300 disinformation distributed via social media and news outlets resulting in vaccine hesitancy.[75-77] As of
301 May 2021 only 16% of pregnant women in the United States had received at least one dose of a COVID-
302 19 vaccine.[78] The problem was compounded by the spread of the SARS-CoV-2 Delta variant in 2021 that
303 caused an increase in disease severity among pregnant women, with almost 20% of the most critically ill
304 hospitalized COVID-19 patients in England being unvaccinated pregnant women. The CDC responded by
305 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 the placental pathology abnormalities such as intervillositis, trophoblast necrosis or increased 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 SARS-CoV2 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 respiratory RNA virus.[85]

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

Recently published clinical studies have confirmed the benefit of maternal vaccination on 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 2,364 babies delivered to vaccinated and unvaccinated mothers during the period between December 1, 2020 and October 31, 2021.[91] A total of 11 stillbirths and 8 livebirths that died in the neonatal period were reported in this study; all occurred in offspring of women who had not received COVID-19 vaccination. By the close of this study in October 2021 the vaccination coverage remained significantly lower among

pregnant women compared with the non-pregnant child-bearing aged female population, with 32.3% of women giving birth in October 2021 having received 2 doses of vaccine compared to 77.4% of all women. A systematic review and meta-analysis of the effects of maternal COVID-19 vaccination on perinatal outcomes based upon 23 studies was released on May 10, 2022.[75] When 66,067 pregnant women who were vaccinated while pregnant for SARS-CoV-2 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 for SARS-CoV-2 from the multicenter Swiss COVI-PREG registry were reported on May 29, 2022.[82] Among 1,012 women in Switzerland who received at least one dose of mRNA vaccine between March 1 and December 27, 2021 there was no increase in adverse pregnancy or neonatal outcomes compared to historical 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 was released. The study demonstrated that infants whose mothers had received the mRNA vaccine while pregnant had a significantly lower risk of testing positive for SARS-CoV-2 during the first four 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 multi-center cohort study by Hui et al. has provided evidence that maternal vaccination for SARS-CoV-2 results in a decreased risk for stillbirth when compared with unvaccinated women.[94] 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 one or more doses of the mRNA COVID-19 vaccine prior to or during pregnancy as compared with 15,171 unvaccinated pregnant women during the period July 1, 2021 to March 31, 2022. The vaccinated women had a significantly lower rate of stillbirth compared to the unvaccinated cohort (0.2% vs 0.8%, aOR 0.18,

354 95%CI 0.09-0.37, P < 0.001). Following stratification for gestational age, this association was statistically
355 significant only for preterm stillbirths.

356 Based upon the data currently available, we postulate that there is a relationship between
357 maternal vaccination for COVID-19, SARS-CoV-2 placentitis and stillbirth. For a virus to reach the
358 placenta, it generally travels through the maternal bloodstream – there is no evidence that SARS-CoV-2
359 is a typical ascending infection that arises from the lower genital tract. In explaining the etiology of
360 SARS-CoV-2 placentitis among 3 stillborn fetuses, Shook et al. suggested that maternal viremia could
361 overcome placental immune defenses at the level of the syncytiotrophoblast.[61] Vaccination for COVID-
362 19 not only lowers viral load and limits viremia, but also decreases vascular and tissue damage, reduces
363 viral dissemination from the lungs to other organs, decreases the incidence of severe disease and death,
364 and suppresses transmission.[95-98] These effects of COVID-19 vaccination during pregnancy can help
365 explain the epidemiological, clinical and pathological studies that indicate reduction of stillbirths among
366 vaccinated women. However, a definitive analysis of this issue has several challenges. Placental
367 examination was not a component of the epidemiological clinical investigations demonstrating
368 vaccination to provide protection to the fetus and neonate from SARS-CoV-2 infection and stillbirth. In
369 addition, there are confounding factors to be considered including the specific type and prevalence of
370 the SARS-CoV-2 variants involved and the possibility that some patients may have been infected by
371 several variants. However, correlating the clinical and epidemiological data with those from studies of
372 placental pathology suggests that one potential, and even likely, mechanism of fetal protection could be
373 from maternal vaccination impeding maternal viremia, development of placental infection and SARS-
374 CoV-2 placentitis.[2] It would seem beyond coincidence that in the multiple reports of SARS-CoV-2
375 placentitis that have been associated with stillbirths and neonatal deaths that none of the mothers had
376 received COVID-19 vaccinations. And although not constituting proof, the authors are not aware, either
377 personally, via collegial networks, or in the published literature, of any cases of SARS-CoV-2 placentitis

causing stillbirths among pregnant women having 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 appears 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 for COVID-19 may be live-saving for the fetus as well as the mother.

References

1. Chinn J, Sedighim S, Kirby KA, et al. Characteristics and outcomes of women with COVID-19 giving birth at US academic centers during the COVID-19 pandemic. JAMA Netw Open 2021;4:e2120456.

2. Schwartz DA. Stillbirth after COVID-19 in unvaccinated mothers can result from SARS-CoV-2 placentitis, placental insufficiency, and hypoxic ischemic fetal demise, not direct fetal infection: potential role of maternal vaccination in pregnancy. Viruses 2022 ;14:458.

3. King A. Doctors investigate several stillbirths among moms with COVID-19. New Scientist 2021. Available from: https://www.the-scientist.com/news-opinion/doctors-investigate-several-stillbirths-among-moms-with-covid-19-68703.

4. Fitzgerald B, O'Donoghue K, McEntagart N, et al. Fetal deaths in Ireland due to SARS-CoV-2 placentitis caused by SARS-CoV-2 alpha. Arch Pathol Lab Med 2022;146:529-37.

398 5. Gurol-Urganci I, Jardine JE, Carroll F, et al. Maternal and perinatal outcomes of pregnant women with
399 SARS-CoV-2 infection at the time of birth in England: national cohort study. Am J Obstet Gynecol
400 2021;225:522.e1–522.e11.

401 6. DeSisto CL, Wallace B, Simeone RM, et al. Risk for stillbirth among women with and without COVID-19
402 at delivery hospitalization—United States, March 2020–September 2021. MMWR Morb Mortal Wkly
403 Rep 2021;70:1640–5.

404 7. Redline RW, Zaragoza M, Hassold T. Prevalence of developmental and inflammatory lesions in
405 nonmolar first-trimester spontaneous abortions. Hum Pathol 1999;30:93-100.
406 8. Abdulghani S, Moretti F, Gruslin A, Grynspan D. Recurrent massive perivillous fibrin deposition and
407 chronic intervillositis treated with heparin and intravenous immunoglobulin: A case report. J Obstet
408 Gynaecol Can 2017;39:676-81.
409 9. Abdulghani S, Moretti F, Nikkels PG, Khung-Savatovsky S, Hurteau-Miller J, Grynspan D. Growth
410 restriction, osteopenia, placental massive perivillous fibrin deposition with (or without) intervillous
411 histiocytes and renal tubular dysgenesis-An emerging complex. Pediatr Dev Pathol 2018;21(1):91-4.
412 10. Cornish EF, McDonnell T, Williams DJ. Chronic inflammatory placental disorders associated with
413 recurrent adverse pregnancy outcome. Front Immunol 2022;13:825075.
414 11. Sebire NJ, Backos M, Goldin RD, Regan L. Placental massive perivillous fibrin deposition associated
415 with antiphospholipid antibody syndrome. BJOG 2002;109:570-3.
416 12. Faye-Petersen OM, Ernst LM. Maternal floor infarction and massive perivillous fibrin deposition. Surg
417 Pathol Clin 2013;6:101-14.
418 13. Weber MA, Nikkels PG, Hamoen K, Duvekot JJ, de Krijger RR. Co-occurrence of massive perivillous
419 fibrin deposition and chronic intervillositis: case report. Pediatr Dev Pathol 2006;9:234-8.

14. Labarrere C, Mullen E. Fibrinoid and trophoblastic necrosis with massive chronic intervillositis: An extreme variant of villitis of unknown etiology. Am J Reprod Immunol Microbiol 1987;15:85–91.

15. Labarrere CA, Bammerlin E, Hardin JW, Dicarlo HL. Intercellular adhesion molecule-1 expression in massive chronic intervillositis: implications for the invasion of maternal cells into fetal tissues. Placenta 2014;35:311-17.

16. Bos M, Nikkels PGJ, Cohen D, et al. Towards standardized criteria for diagnosing chronic intervillositis of unknown etiology: A systematic review. Placenta 2018;61:80-8.

17. Marchaudon V, Devisme L, Petit S, Ansart-Franquet H, Vaast P, Subtil D. Chronic histiocytic intervillositis of unknown etiology: clinical features in a consecutive series of 69 cases. Placenta 2011;32:140-5.

18. Ismail MR, Ordi J, Menendez C, et al. Placental pathology in malaria: a histological, immunohistochemical, and quantitative study. Hum Pathol 2000;31:85-93.

19. Di Gennaro F, Marotta C, Locantore P, Pizzol D, Putoto G. Malaria and COVID-19: Common and Different Findings. Trop Med Infect Dis 2020;5:141.

20. Benachi A, Rabant M, Martinovic J, et al. Chronic histiocytic intervillositis: manifestation of placental alloantibody-mediated rejection. Am J Obstet Gynecol 2021;225:662.e1-11.

21. 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: 285–98.

22. 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;11:17– 22.

23. Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure. BJOG 2003;110: 292– 5.

24. 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;2:100145.

25. Facchetti F, Bugatti M, Drera E, et al. SARS-CoV-2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. EBioMedicine 2020;59:102951.

26. 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;12:1308.

27. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11:3572.

28. 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;145:517–28.

29. 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;145:1341–9.

461 30. Schwartz DA, Baldewijns M, Benachi A, et al. Hofbauer cells and COVID-19 in pregnancy: molecular
462 pathology analysis of villous macrophages, endothelial cells, and placental findings from 22 placentas
463 infected by SARS-CoV-2 with and without fetal transmission**.** Arch Pathol Lab Med 2021;145:1328-40.

464 31. Schwartz DA, Avvad-Portari E, Babál P, et al. Placental tissue destruction and insufficiency from
465 COVID-19 causes stillbirth and neonatal death from hypoxic-ischemic injury. Arch Pathol Lab Med
466 2022;146:660-76.

467 32. Zaigham M, Gisselsson D, Sand A, et al. Clinical-pathological features in placentas of pregnancies
468 with SARS-CoV-2 infection and adverse outcome: case series with and without congenital transmission.
469 BJOG 2022;129:1361-74.

470 33. Konstantinidou AE, Angelidou S, Havaki S, et al. Stillbirth due to SARS-CoV-2 placentitis without
471 evidence of intrauterine transmission to fetus: association with maternal risk factors. Ultrasound Obstet
472 Gynecol 2022;59:813-22.

473 34. Huynh A, Sehn JK, Goldfarb IT, et al. SARS-CoV-2 Placentitis and intraparenchymal
474 thrombohematomas among COVID-19 infections in pregnancy. JAMA Netw Open 2022;5:e225345.

475 35. Delorme-Axford E, Sadovsky Y, Coyne CB. The placenta as a barrier to viral infections. Annu Rev
476 Virol 2014;1:133-46.

477 36. Nahmias AJ, Panigel M, Schwartz DA. The eight most frequent blood-borne infectious agents
478 affecting the placenta and fetus. A synoptic review. Placenta 1994;15(Suppl 1):193-213.

479 37. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and
480 defence. Nat Rev Microbiol 2022;20:67-82.

481 20. Schwartz DA, Levitan D. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infecting
482 pregnant women and the fetus, intrauterine transmission, and placental pathology during the
483 coronavirus disease 2019 (COVID-19) pandemic: it's complicated. Arch Pathol Lab Med 2021;145:925-8.

484 39. Lu-Culligan A, Chavan AR, Vijayakumar P, et al. Maternal respiratory SARS-CoV-2 infection in
485 pregnancy is associated with a robust inflammatory response at the maternal-fetal interface. Med (N Y)
486 2021;2:591-610.e10.

487 40. Taglauer E, Benarroch Y, Rop K,et al. Consistent localization of SARS-CoV-2 spike glycoprotein and
488 ACE2 over TMPRSS2 predominance in placental villi of 15 COVID-19 positive maternal-fetal dyads.
489 Placenta 2020;100:69-74.

490 41. Schwartz DA, Bugatti M, Santoro A, Facchetti F. Molecular pathology demonstration of SARS-CoV-2
491 in cytotrophoblast from placental tissue with chronic histiocytic intervillositis, trophoblast necrosis and
492 COVID-19. J Dev Biol 2021;9:33.

493 42. Schwartz DA, Dhaliwal A. Coronavirus diseases in pregnant women, the placenta, fetus, and
494 neonate. Adv Exp Med Biol 2021;1318:223-41.

495 43. Li Y, Li JZ. SARS-CoV-2 virology. Infect Dis Clin North Am 2022;36:251-65.

496 44. Prebensen C, Myhre PL, Jonassen C, et al. Severe acute respiratory syndrome coronavirus 2 RNA in
497 plasma is associated with intensive care unit admission and mortality in patients hospitalized with
498 coronavirus disease 2019. Clin Infect Dis 2021;73:e799-e802.

499 45. Gutmann C, Takov K, Burnap SA, et al. SARS-CoV-2 RNAemia and proteomic trajectories inform
500 prognostication in COVID-19 patients admitted to intensive care. Nat Commun 2021;12:3406.

501 46. Wang C, Li Y, Kaplonek P, et al. The kinetics of SARS-CoV-2 antibody development is associated with
502 clearance of RNAemia. mBio 2022;e0157722.

503 47. Li Y, Schneider AM, Mehta A, et al. SARS-CoV-2 viremia is associated with distinct proteomic
504 pathways and predicts COVID-19 outcomes. J Clin Invest 2021;131:e148635.

505 48. Tang K, Wu L, Luo Y, Gong B. Quantitative assessment of SARS-CoV-2 RNAemia and outcome in
506 patients with coronavirus disease 2019. J Med Virol 2021;93:3165-75.

507 49. Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral
508 load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients
509 with coronavirus disease 2019. Clin Infect Dis 2020;71:1937-42.

510 50. Roy-Vallejo E, Cardeñoso L, Triguero-Martínez A, et al. SARS-CoV-2 viremia precedes an IL6 response
511 in severe COVID-19 patients: Results of a longitudinal prospective cohort. Front Med (Lausanne)
512 2022;9:855639.

513 51. Fajnzylber J, Regan J, Coxen K, et al. SARS-CoV-2 viral load is associated with increased disease
514 severity and mortality. Nat Commun 2020;11:5493.

515 52. Cardeñoso Domingo L, Roy Vallejo E, Zurita Cruz ND, et al. Relevant SARS-CoV-2 viremia is associated
516 with COVID-19 severity: prospective cohort study and validation cohort. J Med Virol
517 2022;10.1002/jmv.27989.

518 53. Bermejo-Martin JF, González-Rivera M, Almansa R, et al. Viral RNA load in plasma is associated with
519 critical illness and a dysregulated host response in COVID-19. Crit Care 2020;24:691.

520 54. Hagman K, Hedenstierna M, Rudling J, et al. Duration of SARS-CoV-2 viremia and its correlation to
521 mortality and inflammatory parameters in patients hospitalized for COVID-19: a cohort study. Diagn
522 Microbiol Infect Dis 2022;102:115595.

523 55. Rodríguez-Serrano DA, Roy-Vallejo E, Zurita Cruz ND, et al. Detection of SARS-CoV-2 RNA in serum is
524 associated with increased mortality risk in hospitalized COVID-19 patients. Sci Rep 2021;11:13134.

525 56. Kawasuji H, Morinaga Y, Tani H, et al. SARS-CoV-2 RNAemia with a higher nasopharyngeal viral load
526 is strongly associated with disease severity and mortality in patients with COVID-19. J Med Virol
527 2022;94:147-53.

528 57. Jacobs JL, Bain W, Naqvi A, et al. Severe acute respiratory syndrome coronavirus 2 viremia is
529 associated with coronavirus disease 2019 severity and predicts clinical outcomes. Clin Infect Dis
530 2022;74:1525-33.

531 58. Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol
532 2022;226:177-86.

533 59. Edlow AG, Li JZ, Collier AY, et al. Assessment of maternal and neonatal SARS-CoV-2 viral load,
534 transplacental antibody transfer, and placental pathology in pregnancies during the COVID-19
535 pandemic. JAMA Netw Open 2020;3:e2030455.

536 60. Maeda MFY, Brizot ML, Gibelli MABC, et al. Vertical transmission of SARS-CoV2 during pregnancy:
537 A high-risk cohort. Prenat Diagn 2021;41:998-1008.

538 61. Shook LL, Brigida S, Regan J, et al. SARS-CoV-2 placentitis associated with B.1.617.2 (Delta) variant
539 and fetal distress or demise. J Infect Dis 2022;225:754-8.

540 62. Mithal LB, Otero S, Simons LM, et al. Low-level SARS-CoV-2 viremia coincident with COVID placentitis
541 and stillbirth. Placenta 2022;121:79-81.

542 63. Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a
543 systematic review and meta-analysis. Am J Obstet Gynecol 2021;224:35-53.e3.

544 64. Roberts DJ, Edlow AG, Romero RJ, et al. A standardized definition of placental infection by SARS-
545 CoV-2, a consensus statement from the National Institutes of Health/Eunice Kennedy Shriver

National Institute of Child Health and Human Development SARS-CoV-2 placental infection workshop. Am J Obstet Gynecol 2021;225:593.e1-593.e9.

65. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol 2015;213(4 Suppl):S53-69.

66. Erlebacher A. Why isn't the fetus rejected?. Curr Opin Immunol 2001;13:590-3.

67. Maymon E, Romero R, Bhatti G, et al. Chronic inflammatory lesions of the placenta are associated with an up-regulation of amniotic fluid CXCR3: A marker of allograft rejection. J Perinat Med 2018;46:123-37.

68. Goldstein JA, Gallagher K, Beck C, Kumar R, Gernand AD. Maternal-fetal inflammation in the placenta and the developmental origins of health and disease. Front Immunol 2020;11:531543.

69. Lannaman K, Romero R, Chaiworapongsa T, et al. Fetal death: an extreme manifestation of maternal anti-fetal rejection. J Perinat Med 2017;45:851-68.

70. Kim CJ, Romero R, Kusanovic JP, et al. The frequency, clinical significance, and pathological features of chronic chorioamnionitis: a lesion associated with spontaneous preterm birth. Mod Pathol 2010;23:1000-11.

71. Kim MJ, Romero R, Kim CJ, et al. Villitis of unknown etiology is associated with a distinct pattern of chemokine up-regulation in the feto-maternal and placental compartments: implications for conjoint maternal allograft rejection and maternal anti-fetal graft-versus-host disease. J Immunol 2009;182:3919-27.

72. 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;70:285-98.

567 73. Cornish EF, McDonnell T, Williams DJ. Chronic inflammatory placental disorders associated with
568 recurrent adverse pregnancy outcome. Front Immunol 2022;13:825075.

569 74. Lee KA, Kim YW, Shim JY, Won HS, Lee PR, Kim CJ. Distinct patterns of C4d immunoreactivity in
570 placentas with villitis of unknown etiology, cytomegaloviral placentitis, and infarct. Placenta
571 2013;34:432-5.

572 75. Prasad S, Kalafat E, Blakeway H, et al. Systematic review and meta-analysis of the effectiveness and
573 perinatal outcomes of COVID-19 vaccination in pregnancy. Nat Commun 2022;13:2414.

574 76. Shook LL, Kishkovich TP, Edlow AG. Countering COVID-19 vaccine hesitancy in pregnancy: the "4
575 Cs". Am J Perinatol 2022;39:1048-54.

576 77. Iacobucci G. Covid-19 and pregnancy: Vaccine hesitancy and how to overcome
577 it. BMJ 2021;375:n2862.

578 78. Razzaghi H, Meghani M, Pingali C, et al. COVID-19 vaccination coverage among pregnant women
579 during pregnancy - eight integrated health care organizations, United States, December 14, 2020-May 8,
580 2021. MMWR Morb Mortal Wkly Rep 2021;70:895-9.

581 79. Centers for Disease Control and Prevention. New CDC Data: COVID-19 Vaccination Safe for Pregnant
582 People. 2021 Aug 11. Available from: https://www.cdc.gov/media/releases/2021/s0811-vaccine-safe-
583 pregnant.html.

584 80. Kharbanda EO, Vazquez-Benitez G. COVID-19 mRNA vaccines during pregnancy: new evidence to
585 help address vaccine hesitancy. JAMA 2022;327:1451–3.

586 81. Pratama NR, Wafa IA, Budi DS, Putra M, Wardhana MP, Wungu CDK. mRNA COVID-19 vaccines in
587 pregnancy: A systematic review. PLoS One 2022;17:e0261350.

588 82. Moro PL, Olson CK, Clark E, et al. Post-authorization surveillance of adverse events following COVID-
589 19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020
590 - October 2021. Vaccine 2022;40:3389–94.

591 83. Morgan JA, Biggio JR Jr, Martin JK, et al. Maternal outcomes after severe acute respiratory syndrome
592 coronavirus 2 (SARS-CoV-2) infection in vaccinated compared with unvaccinated pregnant patients.
593 Obstet Gynecol 2022;139:107-9.

594 84. Shanes ED, Otero S, Mithal LB, Mupanomunda CA, Miller ES, Goldstein JA. Severe acute respiratory
595 syndrome coronavirus 2 (SARS-CoV-2) vaccination in pregnancy: Measures of immunity and placental
596 histopathology. Obstet Gynecol 2021;138(2):281-3.

597 85. National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS)
598 National Advisory Committee on Immunization: Statement on seasonal influenza vaccine for 2014-
599 2015. Canada Communicable Diseases Report, 2014. http:/www.phac-aspc.gcca/naci-
600 ccni/assets/pdf/flu-grippe-eng.pdf

601 86. Nir O, Schwartz A, Toussia-Cohen S, et al. Maternal-neonatal transfer of SARS-CoV-2 immunoglobulin
602 G antibodies among parturient women treated with BNT162b2 messenger RNA vaccine during
603 pregnancy. Am J Obstet Gynecol MFM 2022;4:100492.

604 87. Trostle ME, Aguero-Rosenfeld ME, Roman AS, Lighter JL. High antibody levels in cord blood from
605 pregnant women vaccinated against COVID-19. Am J Obstet Gynecol MFM 2021;3:100481.

606 88. Shook LL, Atyeo CG, Yonker LM, et al. Durability of anti-spike antibodies in infants after maternal
607 COVID-19 vaccination or natural infection. JAMA 2022;327:1087-9.

608 89. Mithal LB, Otero S, Shanes ED, Goldstein JA, Miller ES. Cord blood antibodies following maternal
609 coronavirus disease 2019 vaccination during pregnancy. Am J Obstet Gynecol 2021;225:192-4.

610 90. Halasa NB, Olson SM, Staat MA, et al. Effectiveness of maternal vaccination with mRNA COVID-19
611 vaccine during pregnancy against COVID-19-associated hospitalization in infants aged <6 months - 17
612 states, July 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71:264-70.

613 91. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in
614 pregnant women in Scotland. Nat Med 2022;28:504-12.

615 92. Favre G, Maisonneuve E, Pomar L, et al. COVID-19 mRNA vaccine in pregnancy: Results of the Swiss
616 COVI-PREG registry, an observational prospective cohort study. Lancet Reg Health Eur 2022;18:100410.

617 93. Carlsen EØ, Magnus MC, Oakley L, et al. Association of COVID-19 vaccination during pregnancy with
618 incidence of SARS-CoV-2 infection in infants. JAMA Intern Med 2022; Jun 1. doi:
619 10.1001/jamainternmed.2022.2442.

620 94. Lui L, Marzan MB, Rolnik DL, et al. Reductions in stillbirths and preterm birth in COVID-19 vaccinated
621 women: a multi-center cohort study of vaccination uptake and perinatal outcome. Am J Obstet Gynecol
622 2022; accepted for publication.

623 95. Levine-Tiefenbrun M, Yelin I, Katz R, et al. Initial report of decreased SARS-CoV-2 viral load after
624 inoculation with the BNT162b2 vaccine. Nat Med 2021;27:790-2.

625 96. Mohamed K, Rzymski P, Islam MS, et al. COVID-19 vaccinations: The unknowns, challenges, and
626 hopes. J Med Virol 2022;94:1336-49.

627 97. Qin Z, Sun Y, Zhang J, Zhou L, Chen Y, Huang C. Lessons from SARS-CoV-2 and its variants. Mol Med
628 Rep 2022;26:263.

629 98. COVID-19 vaccine reduces severity, length, viral load for those who still get infected. University of
630 Arizona News. 30 June 2021. Available from: https://news.arizona.edu/story/covid-19-vaccine-reduces-
631 severity-length-viral-load-those-who-still-get-infected

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634 **FIGURE LEGENDS**

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636 Figure 1. Gross appearance of a sectioned placenta with SARS-CoV-2 placentitis. Massive perivillous
637 fibrin deposition involves the majority of the placental parenchyma.

638 Figure 2. Microscopic image of a placenta with SARS-CoV-2 placentitis and massive perivillous fibrin
639 deposition from a stillborn fetus. Fibrin has completely obstructed the intervillous space and there is
640 severe ischemic necrosis of the chorionic villi. Hematoxylin & eosin, x10.

641 Figure 3. A placenta exhibiting SARS-CoV-2 placentitis. Massive perivillous fibrin deposition is present in
642 which the intervillous space is complete obstructed with fibrin, remnants of histiocytes, and cellular and
643 karyorrhectic debris, preventing maternal blood flow and oxygen delivery to the villi. The
644 syncytiotrophoblast is necrotic, and there is chronic histiocytic intervillositis. Hematoxylin & eosin
645 staining, ×10. Photograph courtesy of Fabio Facchetti, MD, PhD, Pathology Unit, Department of
646 Molecular and Translational Medicine, Università degli Studi di Brescia (Brescia, Italy).

647 Figure 4. Placenta from a stillborn preterm fetus with SARS-CoV-2 placentitis. Immunohistochemistry
648 demonstrates intense positivity for SARS-CoV-2 spike antigen in the syncytiotrophoblast and villous
649 stromal cells. Antibody to SARS-CoV-2 spike protein, ×20

650 Figure 5. Proposed mechanisms for placental infection with SARS-CoV-2 following maternal viremia and
651 development of SARS-CoV-2 placentitis. The high magnification photograph of placenta in the upper
652 right demonstrates a maternal white blood cell, probably a macrophage, staining for SARS-CoV-2 using
653 immunohistochemistry and circulating in the intervillous space and adjacent to infected

654 syncytiotrophoblast. Abbreviations: CV=chorionic villus; IVS=intervillous space;

655 SYN=syncytiotrophoblast.