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

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An emerging infectious disease is caused by a newly identified microbial agent or one whose incidence has increased in the previous 20 years. In particular, newly emergent viral diseases always cause great anxiety, not only in the medical and public health communities but also among those individuals and groups that are at risk for acquiring infection. This is often most pronounced among women who are pregnant or planning to become pregnant, and who are not just anxious for themselves but for the well-being of their unborn infants. Long considered to be among the most potentially vulnerable groups of persons during an infectious disease outbreak, pregnant women and infants are not generally included in the conceptualization, design, and clinical testing and distribution of novel therapies and vaccines for new viral agents, thus creating a public health and human rights dilemma.[1–3] This is especially important because new and reemergent viral diseases historically have adversely affected pregnant women, often causing greater harm to them than to those infected women who are not pregnant. Influenza, Ebola virus, hepatitis E, and varicella are good examples because these viruses may have a more severe clinical course, increased complication rate, and higher case-fatality rate among pregnant women than in nonpregnant individuals, and the recently identified flavivirus infection caused by the Zika virus causes most of its morbidity during pregnancy.[4–7]

The pandemic of coronavirus disease 2019 (COVID-19) that has encompassed the world has had a profound effect on both pregnant women and birthing. The initial studies emanating from China in the beginning phase of the pandemic suggested that although pregnant women could develop infection with the novel coronavirus, termed *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), it appeared that most infected mothers had mild or nonexistent symptoms and did not become more ill than did nonpregnant women of the same age.[8–11] As occurred during previous epidemics from such emerging coronaviruses as SARS and Middle East respiratory syndrome (MERS),[12] as well as some other RNA respiratory viruses,[13] there was no definitive mother-to-infant (vertical) transmission recognized early in the COVID-19 pandemic. However, with continued spread of the virus and increasing numbers of patients studied throughout the world, not only was it becoming clear that COVID-19 could produce a spectrum of severe and even life-threatening disease in pregnant women,[14,15] but there were increasing descriptions of newborn infants who tested positive for SARS-CoV-2 shortly after delivery.[16–18] At that time, the etiology of these neonatal infections was unknown—they may have resulted from postnatal infection from environmental sources or been due to vertical (mother-to-infant) transmission occurring before, during, or following delivery.[19–21] For reasons of best clinical practice, infection control, and scientific knowledge, it was important to determine whether these represented vertically acquired infections, and if they did, how and when mother-to-infant transmission was occurring. Vertical transmission can result from several different pathways of infection. These include intrauterine transmission, either transplacentally from the maternal bloodstream or an ascending route from the cervical vaginal canal; intrapartum transmission; or postpartum infection from contact with infected maternal fluids or secretions.

Pathologic evaluation of the placenta, the largest of fetal organs, has been an instrumental technique in elucidating mechanisms of transmission of previous emerging infectious agents from pregnant women to the fetus. Analyses of placentas from mothers with SARS-CoV-2 infection were

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initiated to help resolve these issues, but their results were inconclusive; they demonstrated a spectrum of pathology findings that varied significantly between studies. In some investigations there was evidence of maternal vascular malperfusion,[22] in others there was evidence of fetal vascular malperfusion,[23] and in some, both[24–26]; other investigators described inflammatory lesions, including chronic histiocytic intervillositis, villitis, funisitis, and chorioamnionitis[24–26]; and others found no specific findings of COVID-19 in placentas from infected women.[27–29] One publication[29] was titled "SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology. . .," adding to the spectrum of differing findings and conclusions of the placental pathology from coronavirus infection. However, in all of these studies, the large majority of placentas examined were not infected with SARS-CoV-2 and were from neonates testing negative for SARS-CoV-2 infection.

Schwartz and colleagues[30] proposed pathology diagnostic criteria for the diagnosis of intrauterine transplacental transmission of SARS-CoV-2 from an infected mother. These criteria were based on mother-neonatal dyads testing positive for SARS-CoV-2 together with demonstration of the coronavirus in the fetal cells of the placenta using such molecular pathology techniques as immunohistochemistry for viral antigens and RNA in situ hybridization for viral nucleic acid.[31] Eventually, cases of probable transplacental infection of fetuses with SARS-CoV-2 were identified that met the published clinical and pathologic criteria for placental infection and intrauterine maternal-fetal infection. Thus, SARS-CoV-2 became the newest TORCH (toxoplasma, other, rubella, cytomegalovirus, herpes) agent. The initial analysis of the published findings from these transmitting placentas disclosed that their pathology findings were much more uniform than the variable findings present in uninfected placentas from pregnant women with SARS-CoV-2.[32] Remarkably, the placentas from SARS-CoV-2–infected maternal-neonatal dyads all showed 3 unusual but concurrent abnormalities: trophoblast necrosis, chronic histiocytic intervillositis, and coronavirus infection of the syncytiotrophoblast, using immunohistochemistry, RNA in situ hybridization, or both.

In this journal there have been 2 articles published recently describing placental pathology findings in pregnant women infected with SARS-CoV-2. At first glance, these 2 articles, one by Schwartz et al[33] and the other by Levitan et al,[34] may appear to show disparate and contradictory findings. However, given the recent insights into what initially appeared to be discrepancies in the effects of SARS-CoV-2 on the placenta, these 2 articles are not only complementary but support the premise that certain placental pathology findings in COVID-19 are largely the result of infection of the placenta itself. These articles examine placental pathology from 2 very different cohorts of pregnant women having SARS-CoV-2 infection: one study from the perspective of examining only infected placentas from infected neonates with probable intrauterine coronavirus transmission, and the other from uninfected neonates with uninfected placentas.

In their article, Schwartz et al[33] hypothesized that the placental pathology occurring in those placentas infected with SARS-CoV-2 and which transmitted the virus to the fetus would differ from the spectrum of pathology in uninfected placentas. The multinational team of authors evaluated 11 placentas from 5 countries in which there was suspected intrauterine transplacental transmission of SARS-CoV-2 from an infected mother to the fetus based on published criteria.[30] This cohort included 6 liveborn neonates, 4 stillborn infants, and 1 infant from an elective pregnancy termination, all infected with SARS-CoV-2, in which both standard and molecular methods were used to characterize the spectrum of placental pathology features. In all placentas obtained from liveborn and stillborn infants, the primary cell type infected by SARS-CoV-2 was the syncytiotrophoblast, as documented by immunohistochemistry, RNA in situ hybridization, or, in some cases, both techniques. All 6 placentas from liveborn neonates contained an uncommon, if not rare, microscopic finding termed *chronic histiocytic intervillositis*, an abnormality that had never previously been regularly associated with an infectious process and which occurs in only 6 of 10 000 pregnancies during the second and third trimesters.[35] All 6 placentas also demonstrated syncytiotrophoblast necrosis. Among the 5 stillborn or electively terminated infants, the placentas contained the identical grouping of pathology findings, as did those of the 6 liveborn neonates: chronic histiocytic intervillositis, syncytiotrophoblast necrosis, and positivity of the syncytiotrophoblast for SARS-CoV-2 using RNA in situ hybridization or immunohistochemistry. In addition to all 11 placentas having this group of findings, most of them also demonstrated increased fibrin deposits, with some that were consistent with massive perivillous fibrin deposition. The 11 infected placentas in this article showed remarkable consistency of pathology findings, beyond the level of coincidence, and all occurring in placentas that were believed to be transmitting the coronavirus to the fetus prior to delivery.

The article by Levitan et al[34] took a quite different approach to examining placental pathology in pregnant women with SARS-CoV-2 infection. Conducted early in the pandemic, this study evaluated placentas from 65 pregnant women with SARS-CoV-2 infection who had received a diagnosis using nasopharyngeal swab samples and reverse transcription–polymerase chain reaction. The authors aimed to answer 2 questions; the first—"Is maternal SARS-CoV-2 infection associated with a specific histopathologic finding or set of findings?"—relied on gross and microscopic evaluation of the collected placentas. The control group consisted of 85 placentas from SARS-CoV-2–negative women who, aside from SARS-CoV-2 status, were remarkably similar to the positive cohort from a clinical standpoint. Histologic examination of the placentas revealed no statistically significant difference in the prevalence of 21 unique histopathologic findings between the groups, mirroring the results of similar works.[28,29] As such, the study failed to support earlier[23–27] and current[22] contentions that fetal vascular malperfusion and/or maternal vascular malperfusion may represent SARS-CoV-2–associated placental insults. Afterward, immunohistochemical staining of select tissue sections for SARS-CoV-2 nucleocapsid protein was performed to facilitate the second goal of the investigation, namely, to look for evidence of placental infection by the virus itself. None of the 64 placentas that underwent staining showed any evidence of virus within syncytiotrophoblast or any other cell type. Of note, none of the 66 liveborn neonates tested positive for SARS-CoV-2 within 1 day of life. Hence, the authors concluded that maternal SARS-CoV-2 infection alone does not seem to lead to any disease-specific placental histopathology. Likewise, the study results seemed to suggest that direct invasion of placental tissue by SARS-CoV-2 is a relatively

uncommon phenomenon. The study's failure to show a viral footprint in any of the examined placentas succeeded in buttressing the growing evidence that placental infection by SARS-CoV-2 is associated with a completely different histopathologic signature. Indeed, chronic histiocytic intervillositis and trophoblast necrosis—2 findings shown to be present in transmitting placentas[33]—were conspicuously absent from the placental cohorts of Levitan et al.[34]

The observations in these articles, 2 dramatically different sets of pathology findings and neonatal outcomes from cohorts of placentas with different inclusion criteria, highlight the conundrum of explaining differences in how the placenta reacts to SARS-CoV-2 when the pregnant woman becomes infected with the coronavirus. How should we reconcile the differences in placental pathology findings in these reports? Although it may be premature to state with complete confidence, the observations made in these articles and others leads to several preliminary conclusions:

1. The syncytiotrophoblast is probably the most susceptible and frequent cell type composing the maternal-fetal interface to be infected with SARS-CoV-2.

The syncytiotrophoblast expresses angiotensin-converting enzyme 2 (ACE2), the cell surface receptor for SARS-CoV-2, as well as the protease TMPRSS2, which cleaves the viral spike protein to facilitate infection.[36,37] In those placentas with coronavirus infection demonstrated by immunohistochemistry and/or RNA in situ hybridization, the intensity of syncytiotrophoblast staining is suggestive of a high viral load, higher even than that seen with Ebola virus infection.[38] However, it appears clear that in the overwhelming proportion of placentas in which the pregnant woman is infected with SARS-CoV-2, the syncytiotrophoblast is not infected.

2. SARS-CoV-2 infection of the syncytiotrophoblast is typically accompanied by 2 unusual placental pathology findings, chronic histiocytic intervillositis and trophoblast necrosis, in both liveborn and nonviable infants.

Following the preparation and report of the paper by Schwartz et al,[33] additional published reports[39–42] have demonstrated the same triad of placental pathology findings, and one of the authors (DAS) is aware of additional unpublished cases. Among pregnant women infected with the coronavirus, and in the absence of syncytiotrophoblast infection with SARS-CoV-2, the other 2 components of the pathology triad (chronic histiocytic intervillositis and trophoblast necrosis) appear not to occur.

3. Intrauterine infection of the fetus with SARS-CoV-2 can result from transplacental transmission of the virus, but it is very uncommon.

Estimates of the probability of a pregnant woman infected with SARS-CoV-2 having a neonate who tests positive for the virus vary from less than 1% up to 5%.[32] A recent meta-analysis estimated that among all neonates testing positive for SARS-CoV-2, 5.7% have confirmed congenitally transmitted infection occurring prior to delivery.[43] In cases examined thus far, transplacental transmission of SARS-CoV-2 is associated with a demonstrable and consistent triad of coexistent pathology findings: chronic histiocytic intervillositis, trophoblast necrosis, and coronavirus infection of the syncytiotrophoblast as identified using molecular pathology techniques. When these findings at the maternal-fetal interface are absent, there has been no documented transplacental infection.

4. The placental pathology findings in COVID-19 appear to be mostly associated with the presence or absence of SARS-CoV-2 infection of the placenta, and specifically infection of the syncytiotrophoblast.

In cases where the syncytiotrophoblast is uninfected, transplacental transmission of the virus appears unlikely. These placentas will instead be normal or have elements of fetal and/or maternal vascular malperfusion or other findings that may or may not be related to maternal infection from SARS-CoV-2.

5. The triad of chronic histiocytic intervillositis, trophoblast necrosis, and SARS-CoV-2 infection of the syncytiotrophoblast constitutes a placental pathology risk factor for transplacental transmission of the coronavirus to the fetus.

This is arguably one of the first times that placental pathology findings have been considered to be significant risk factors for maternal-fetal transmission of a viral TORCH agent.

The investigation of placentas from pregnant women and infants with SARS-CoV-2 infections is still in its early stages, and it is to be expected that there will be variations and exceptions to the findings and hypotheses that we have proposed. It should not be anticipated that every placenta demonstrating SARS-CoV-2 infection of the syncytiotrophoblast will have the other 2 placental pathology findings of the triad. And similar to other TORCH infections, not every placenta infected with SARS-CoV-2 can be expected to have resulting fetal infection. In addition, because the maternal-fetal interface possesses multiple mechanisms in place to serve a protective function against microbial invasion, it is to be expected that in some cases there will be virus present in placental cells, and possibly even trophoblast necrosis and chronic histiocytic intervillositis, in the absence of fetal infection. For example, there has been one placenta reported as having the triad of placental pathology findings (syncytiotrophoblast necrosis and infection with SARS-CoV-2 and chronic histiocytic intervillositis), but in this case the neonate was initially tested for coronavirus on the fourth day of life and was negative.[43] Similar to other TORCH agents, such as cytomegalovirus, there must be a time interval that occurs between maternal infection, initial exposure of the cells at the maternal-placental interface to the virus, entry of the virus into the trophoblast or other fetal-derived cells, viral replication, transit of the virus into the fetal bloodstream, and subsequent fetal infection. Depending on covariables relating to the host, tissue, and virus, this process of transplacental transmission could take many days to even weeks in some cases.[37] An example of this potential delay between infection of the pregnant woman and the placenta may be illustrated in a recent communication describing an 11-week interval between the initial maternal infection with SARS-CoV-2 and delivery in which placental infection was found by immunohistochemistry for viral nucleocapsid protein associated with chronic histiocytic intervillositis and other abnormalities.[44] Because so few placentas become infected with SARS-CoV-2, there are likely mechanisms that impede this process in most cases which may involve

innate immune factors and the intrinsic defense system of the placenta, including the maternal-fetal interface. The role of such immunologically active cells as villous stromal macrophages, termed Hofbauer cells, is being investigated but remains undetermined.[45] With additional analysis and research, it is hoped that greater understanding of the role played by the placenta in permitting or preventing perinatal infection with SARS-CoV-2 will be forthcoming.

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