# Pregnant Women Diagnosed With COVID-19 and Stillbirths - New Findings

February 10, 2022

**Julie McDowell:**

As the COVID-19 pandemic continues, perinatal deaths remain an important question, particularly because the mechanism of death remains unclear. A new study just published in the Archives of Pathology & Laboratory Medicine found that pathology abnormalities composing SARS-CoV-2 placentitis caused widespread and severe placental destruction that can result in stillbirth. To the best that researchers could determine, all of the mothers in this study were unvaccinated.

In this CAPcast, Dr. David Schwartz, lead author of this study, discusses the research and what conclusions pathologists and the public should take away from these findings. Dr. Schwartz, let's start with an explanation from you on the key findings from your research.

**Dr. David Schwartz:**

That sounds great, Julie. Thank you for having me here. Let me just mention that at this point the pandemic has been going on for two years, and we have been following complications occurring in pregnant women and newborns. But stillbirth was not initially recognized as being a complication of COVID-19 infection in pregnant women. However, as the new variants of the virus rose and spread throughout the world, and especially with the onset of the Delta variant, it was noted by pathologists, as well as obstetricians and other maternal healthcare providers, that there appeared to be increasing numbers of stillborn fetuses that were occurring in pregnant mothers with COVID-19.

As you mentioned at the beginning, Julie, because the mechanism of intrauterine death of fetuses in mothers with SARS-CoV-2 infection was not well known, my colleagues and I decided to investigate this occurrence. So my 43 co-authors on this article and myself examined 68 cases of stillbirth or early neonatal death with the following inclusion criteria for the study. Number one, the women had a positive test result for SARS-CoV-2 during pregnancy using a reverse transcriptase-polymerase chain reaction test prior to delivery. Number two, an obstetric outcome of either stillbirth or early neonatal death. And finally, the placenta was submitted for pathology examination and diagnosed with SARS-CoV-2 infection by direct visualization of fetal-derived placental cells using immunohistochemistry for SARS-CoV-2 antigens, and/or RNA in situ hybridization for SARS-CoV-2 nucleic acid, and/or fluorescence in situ hybridization, and/or PCR or a combination of all these techniques.

We also wanted to assess the frequency of the three components of what has now been termed SARS-CoV-2 placentitis. And they are increased fibrin, trophoblast necrosis, and an entity we call chronic histiocytic intervillositis. A unique part of this study was estimating the percentage of placental destruction in each case based upon the correlation of both the gross and the microscopic features of the placentas. And finally, we wanted to confirm our previous research findings on the distribution of the virus in the different placental cell types.

Now this study took a very long time to do, but interestingly, as we were concluding the enrollment of the cases, of the 68 cases, and analyzing the data in November of 2021, the CDC issued an article in its publication MMWR, stating that women with COVID-19 were at increased risk for stillbirth compared with women without COVID-19, and that the magnitude was greatest during the Delta variant predominance around the world. Excuse me. So this was very significant because it had been somewhat controversial before this statement from the CDC whether or not stillbirth really was a risk factor in pregnant women with COVID-19.

So when we finished the study, there were 64 stillborn fetuses and four early neonatal deaths from 12 countries in our cohort. And the results showed that all placentas, all 68 placentas, demonstrated a diffuse destructive pathological process. All 68 placentas had increased fibrin deposition and villous trophoblast necrosis, and 66 had chronic histiocytic intervillositis, the three findings that constitute SARS-CoV-2 placentitis. 63 placentas had massive per villous fibrin deposition, an uncommon finding in which large parts of the placenta become embedded in fibrin and are necrotic. And it was just a surprise to us that among the 68 placentas, severe destructive placental disease from SARS-CoV-s placentitis averaged 77.7% tissue involvement. In other words, over three quarters of the placental parenchyma had been involved with SARS-CoV-2 placentitis and destroyed.

Now other findings, beside the SARS-CoV-2 placentitis, included the presence of hemorrhages and multiple intervillous thrombi in 37%. And chronic villitis in 32%, and these likely contributed to the outcomes. The most common placental cell to be involved with SARS-CoV-2 was the syncytiotrophoblast, which confirmed their previous results. It stained positive in all of the placentas in which testing was performed that could localize the infected cell type. Other cells that were found to be positive included the cytotrophoblast in 12%; Hofbauer cells, which are the native macrophage population in the chorionic villi, were positive in 5%; villous stromal cells in 5%; maternal cells in the intervillous space in 5%; and villous capillary endothelial cells in 3%.

Among the 64 stillborn fetuses in this study, death occurred at a mean gestational age of 30 weeks, which was also the modal value. And so death was occurring predominantly in preterm infants. Delivery of the 64 still births ranged from 15 weeks up to 39.2 weeks in gestation. Of the four cases of neonatal death, they were all delivered preterm at a mean gestational age of 30.8 weeks. Now among these 68 cases there were 30 autopsies performed, and in the majority there were no significant fetal abnormalities, except in some for finding evidence of intrauterine hypoxia and asphyxia. Among all 68 cases, SARS-CoV-2 was detected from a body specimen in 16 of the 28 cases tested, most frequently nasopharyngeal swabs. Four autopsied stillborns had SARS-CoV-2 identified in internal organs. But most importantly, there was no evidence from these autopsies that SARS-CoV-2 involvement of the fetus had a role in causing the fetal deaths.

So this large study, which is the largest study of stillborns from women with COVID-19 and SARS-CoV-s placentitis, this study accomplished three major things. It showed that when the placenta was infected, SARS-CoV-2 placenititis occurred in virtually 100% of stillborn fetuses in early neonatal deaths. Secondly, it demonstrated that greater than one half of the placenta with a mean of 77% were affected and destroyed by SARS-CoV-2 placentitis, which effectively rendered the placenta incapable of carrying out its function and supporting fetal life. And finally, it concluded that the destructive effect of SARS-CoV-2 on the placenta leads to fetal and neonatal demise via a process of placental malperfusion and insufficiency, resulting in a hypoxic-ischemic death. And in fact, the extent of placental destruction in these cases was so severe that it could be argued that whether the fetus was infected or not was almost irrelevant.

**Julie McDowell:**

What do you want pathologists to take away from these findings?

**Dr. David Schwartz:**

Oh, well, that's a great question. Julie. Pathology as a specialty, as I'm sure you know, has had a key role in our understanding of the pathological diagnosis and consequences of emerging infectious diseases, whenever they've occurred. And in particular, pathology has made significant contributions to our understanding of emerging infections in pregnant moms and how the organisms affect the placenta fetus and newborn, and also when in delineating the mechanisms of maternal fetal transmission.

From the standpoint of practicing pathologists, I believe that this article, as well as previous ones, highlights the entity of SARS-CoV-2 placentitis. As I've mentioned, it's the combination of three unusual findings, increased fibrin and massive perivillus fibrin deposition, trophoblast necrosis, and chronic histiocytic intervillositis. When seen at a placenta during this time with the COVID pandemic, these findings should raise a suspicion to the pathologist for SARS-CoV-2 infection, whether it's occurring in the placenta of a live born or a stillborn baby. Typically, but not always, there will be a clinical history that reinforces the suspicion. And of course, it's always helpful to contact the clinical management team to discuss the SARS-CoV-2 status of the mother.

In any case of a stillborn fetus or a neonatal death having a placenta with these findings, the placenta can be further investigated for evidence of the virus. The best methods are immunohistochemistry and RNA in situ hybridization. In my experience, it is not challenging to identify positive viral signal in these infected placentas. It's very different than what I've seen a few years ago with the Zika virus pandemic, where it was very, very difficult to identify the Zika virus in infected placentas. In our COVID-19 cases, the syncytia trophoblast is by far the most common cell type that is infected. And much, much less commonly one can also see positive staining in the cytotrophoblast, Hofbauer cells, and the villous endothelial and stromal cells.

At this point in time, the diagnostic reagents for performing immunohistochemistry and RNA and situ hybridization are commercially available for purchase. And several commercial laboratories will also provide this testing on formal and fixed paraffin-embedded tissues. Of course, we have to remember that not all stillbirths occurring in mothers with COVID-19 will be the result of coronavirus infection, and of course other causes, including other infectious agents, need to be considered.

**Julie McDowell:**

So what about the public? What would you like patients to take away from these findings?

**Dr. David Schwartz:**

Well, again, that's a very good question, Julie. I'm contacted constantly by patients asking about this. And thankfully, placental infection with SARS-CoV-2 in pregnant moms with COVID-19 is very uncommon, although it's now been shown that the virus can pass through the placenta and infect the fetus prior to delivery, this is also very uncommon. We don't really have a good knowledge yet of the risk factors for these events. Even in those cases where the placenta is infected, as it was in this series of 68 cases that we're publishing, the babies generally do well unless there is extensive placental destruction as we reported in this article. And so my colleagues and I have certainly seen placentas that show infection, and yet the babies are live born and they do well.

Many of us believe that, based on the findings in this article, as well as other publications, that being vaccinated before or during pregnancy for COVID-19 may be beneficial in either reducing the likelihood or even preventing placental infection with coronavirus. And of course, multiple studies now have demonstrated that the vaccines that we're currently using in the United States are very safe for use in pregnancy. And we believe that not only can they be lifesaving for the mom, but also for the baby.

**Julie McDowell:**

What about future research? How are you following up this research?

**Dr. David Schwartz:**

Well, we just completed this study recently, and again, there were quite a few surprises and new findings in this study. And so some of the things that we're looking at would include the effect of maternal vaccination on preventing SARS-CoV-2 placentitis. We're looking at the occurrence of the virus in mother's bloodstream, what we call viremia, and its association with placental and fetal infection. And in addition, we're doing some additional placental work trying to further characterize the placental pathology findings, as well as looking at the effects of the virus on multi-fetal pregnancies.

**Julie McDowell:**

Well, thank you for discussing this research, Dr. Schwartz. Anything you want to add before we close our interview?

**Dr. David Schwartz:**

Well, if you don't mind, do we have time?

**Julie McDowell:**

Yep.

**Dr. David Schwartz:**

Great. Well, I would just like to add that the College of American Pathologists and the Archives of Pathology & Laboratory Medicine have really been at the forefront of responding to newly discovered infectious agents and outbreaks of emerging infections for decades. Special issues of the Archives, and I may be the only one old enough to remember these, but there were special issues devoted to the topic of emerging infections 25 years ago, issued in 1996 and in 1997. And then in 2016 the editorial staff of the Archives responded immediately to the Zika virus pandemic by organizing and then publishing the first special issue of any journal that was devoted to that new infection. So thank you very much. I appreciate talking with you.

**Julie McDowell:**

Well, thanks again, Dr. Schwartz. Dr. Schwartz's findings are now posted on the Archives of Pathology & Laboratory Medicine's website under Early Online Release articles. The website is archivesofpathology.org, and Dr. Schwartz's article is entitled Placental Tissue Destruction and Insufficiency from COVID-19 Causes Stillbirth and Neonatal Death from Hypoxic-Ischemic Injury: A Study of 68 Cases with SARS-CoV-2 Placentitis from 12 Countries.

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