# Placental Histopathology Findings during SARS-CoV-2 Infection in Haji Adam Malik General Hospital Medan Indonesia: Series of 28 Cases in 2021

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**Abstract: Background:** During pregnancy, SARS Coronavirus 2 infection may cause an abnormal development of the placenta, thus influencing maternal and fetal outcomes. Placental pathology in the setting of maternal SARS-CoV-2 infection remains a topic of great interest because the raising concern for vertical transmission and earlier studies have shown mixed results

**Objective:** We present series of 28 placentas of SARS-CoV-2 positive women who had been diagnosed by RT PCR in Haji Adam Malik General Hospital as one major goverment hospital for COVID-19 management in Medan, North Sumatera, Indonesia from February- August 2021.

**Methods:** All placentas were microscopically examined with H&E-stained sections, which usually included full-thickness sections that included fetal and maternal surfaces and one section with two umbilical cord sections and membrane rolls.

**Results:** Pathologic findings were divided into maternal vascular malperfusion, fetal vascular malperfusion, chronic inflammatory lesions, amniotic fluid infection sequence, increased perivillous fibrin, intervillous thrombi, increased subchorionic fibrin, meconium-laden macrophages within fetal membranes, and chorangiosis. Mostly, the placentas showed prominent signs of increased fibrin deposition in perivillous and intervillous thrombus (92,9 % and 82,1%), but not many showed lymphohistiocytic villitis (10,7%) respectively, as reported in other studies.

**Conclusions:** Limited conclusions can be drawn about the effect of maternal SARS-CoV-2 infection on placental pathology. Based on the data in this study, we report general histopathological features, which include maternal vascular malperfusion, fetal vascular malperfusion, inflammation and thrombus in placentas with COVID-19 infection. A prospective cohort study with a larger sample population with thorough placental examination is needed to understand the impact of SARS-CoV-2 on the placenta, pregnancy and possible fetal sequelae.

**Keywords:** placenta, histopathology, COVID-19, SARS-CoV-2, pregnancy

## I. INTRODUCTION

On March 11, 2020, due do the rapid escalation of the coronavirus disease 2019 (COVID-19) outbreak, the World Health Organization (WHO) declared a pandemic. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta coronavirus similar to SARS-CoV and MERS-CoV, with multiple possible transmission routes and characterized by a high infectivity.[1]

SARS-CoV-2 is an enveloped single positive stranded RNA virus responsible for the current pandemic of severe respiratory infections worldwide termed COVID-19. SARS-CoV-2 infects tissues via its receptor, ACE2, and entry into cells requires spike protein cleavage by the serine protease TMPRSS2. Although many reports of COVID-19 in pregnancy describe complications, such as preterm birth, vertical transmission is apparently extremely rare. Few reports of pregnancy and COVID-19 address placental infection rigorously and, to date, only two reports have demonstrated direct viral infection of the placenta.[2]

Few studies have reported data describing the effects of coronavirus disease 2019 on placental morphology and histology in infected pregnant patients.

## II. MATERIAL AND METHODS

Placentas received from January-August 2021 by the Anatomical Pathology Instalation at Haji Adam Malik General Hospital Medan were randomly picked to be included in this report, which consisted of 28 cases. They underwent fixation for 24 hours prior to dissection. Typical sections were fixed in formalin, processed into paraffin blocks, and stained with usual Hematoxylin and Eosin stain.

Clinical information was retrieved from the electronic medical record or patient status sheet. Testing for COVID-19 was not performed on placental tissue. However, all mothers were tested via RT-PCR at Haji Adam Malik General Hospital Medan.[3]

## III. RESULTS

In this study, obtained as many as 28 cases of tissue paraffin blocks that have complete medical record data. All expectant mothers at our institution are tested for COVID-19 even if asymptomatic and all mothers in this study tested positive.

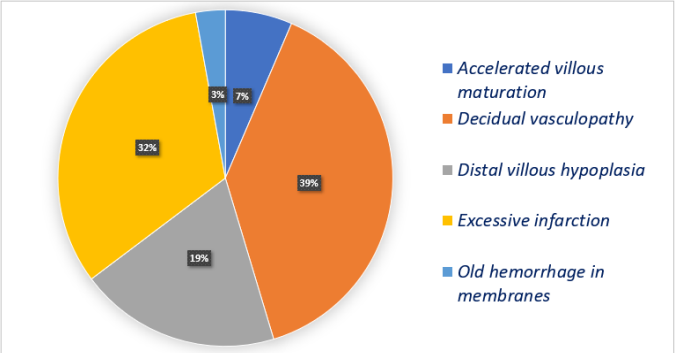
Table 1. Clinical Information

| Variable | Mean | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|
| Age | 29.46 | 6.47 | 30.00 | 17.00 | 42.00 |
| IMT | 22.60 | 1.72 | 22.24 | 20.40 | 26.67 |
| Haemoglobin | 11.75 | 2.09 | 11.85 | 8.30 | 17.40 |
| Haematocryte | 35.17 | 6.11 | 35.10 | 26.40 | 54.00 |
| Leucocyte | 12,800.36 | 7,127.99 | 10,285.00 | 6,180.00 | 38,410.00 |
| PLT | 274,750.00 | 104,751.78 | 248,500.00 | 136,000.00 | 495,000.00 |
| Neutrofil | 10.50 | 6.32 | 8.69 | 3.94 | 33.69 |
| Lymphocyte | 1.48 | 0.84 | 1.44 | 0.46 | 5.00 |
| D dimer | 1,891.36 | 1,358.43 | 1,320.00 | 255.00 | 4,001.00 |
| Fibrinogen | 565.89 | 180.51 | 531.50 | 213.04 | 900.00 |

Table 2. Pathology

| Placental Histopathologic Findings | | | n | % |
|---|---|---|---|---|
| Maternal Vascular Malperfusion | Accelerated villous maturation | Present | 2 | 7.1 |
| | | Absence | 26 | 92.9 |
| | Decidual vasculopathy | Present | 12 | 42.9 |
| | | Absence | 16 | 57.1 |
| | Distal villous hypoplasia | Present | 6 | 21.4 |
| | | Absence | 22 | 78.6 |
| | Excessive infarction | Present | 10 | 35.7 |
| | | Absence | 18 | 64.3 |
| | Old hemorrhage in membranes | Present | 1 | 3.6 |
| | | Absence | 27 | 96.4 |
| Fetal vascular malperfusion | Villous stromal vascular karyorrhexis | Present | 1 | 3.6 |
| | | Absence | 27 | 96.4 |
| | Avascular villi | Present | 0 | .0 |
| | | Absence | 28 | 100.0 |
| | Intramural fibrin deposition | Present | 22 | 78.6 |
| | | Absence | 6 | 21.4 |
| | Stem vessel obliteration | Present | 1 | 3.6 |
| | | Absence | 27 | 96.4 |
| Chronic inflammatory lesions | Chronic villitis | Present | 3 | 10.7 |
| | | Absence | 25 | 89.3 |
| | Chronic deciduitis | Present | 11 | 39.3 |
| | | Absence | 17 | 60.7 |
| Amniotic fluid infection sequence | Maternal response_Chorionitis | Present | 11 | 39.3 |
| | | Absence | 17 | 60.7 |
| | Fetal response_Amnionitis | Present | 4 | 14.3 |
| | | Absence | 0 | .0 |
| | Increased perivillous fibrin | Present | 23 | 82.1 |
| | | Absence | 5 | 17.9 |
| | Intervillous thrombus | Present | 26 | 92.9 |
| | | Absence | 2 | 7.1 |
| | Increased subchorionic fibrin | Present | 21 | 75.0 |
| | | Absence | 7 | 25.0 |
| Miscellaneous pathology | Meconium laden macrophages | Present | 0 | .0 |
| | | Absence | 28 | 100.0 |
| | Chorangiosis_Chorangioma | Present | 14 | 50.0 |
| | | Absence | 14 | 50.0 |
| | Chorangiosis_Chorangioma_2 | Present | 1 | 3.6 |
| | | Absence | 27 | 96.4 |
| Villitis | | Present | 2 | 7.1 |
| | | Absence | 26 | 92.9 |
| Umbilical vasculitis | | Present | 8 | 28.6 |
| | | Absence | 20 | 71.4 |
| Retroplacental thrombus | | Present | 6 | 21.4 |
| | | Absence | 22 | 78.6 |
| Increased Syncytial Knots | | Present | 6 | 21.4 |
| | | Absence | 22 | 78.6 |
| Villous agglutination | | Present | 8 | 28.6 |
| | | Absence | 20 | 71.4 |
| Villous infarction | | Present | 4 | 14.3 |
| | | Absence | 24 | 85.7 |

Table 3. Maternal Vascular Malperfusion
(28 placentas in H. Adam Malik General Hospital Medan Feb-Aug 2021)



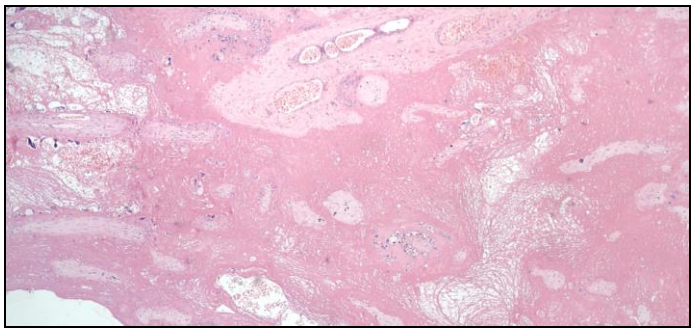
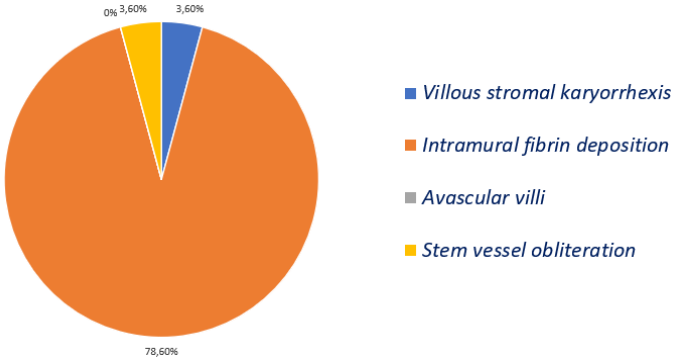


Figure 1. Section of the placenta with excessive infarction (H&E; x100).

Table 4. Fetal vascular malperfusion
(28 placentas in H. Adam Malik General Hospital Medan Feb-Aug 2021)



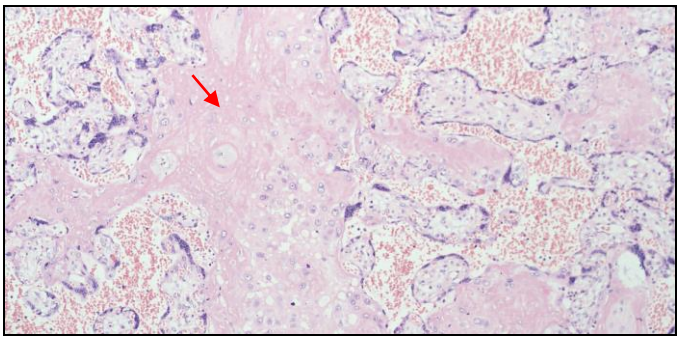
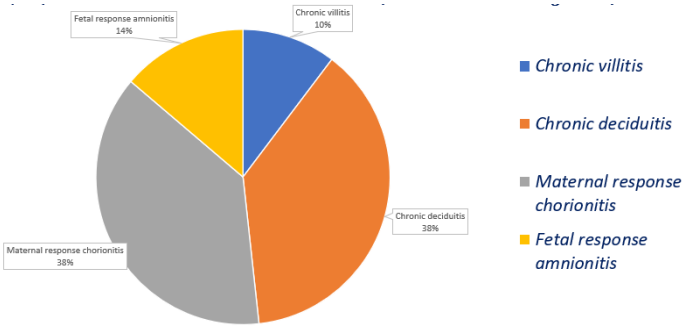



Figure 2. Intramural fibrin appearance (H&E; x 100).

Table 5. Inflammatory Lesions
(28 placentas in H. Adam Malik General Hospital Medan Feb-Aug 2021)



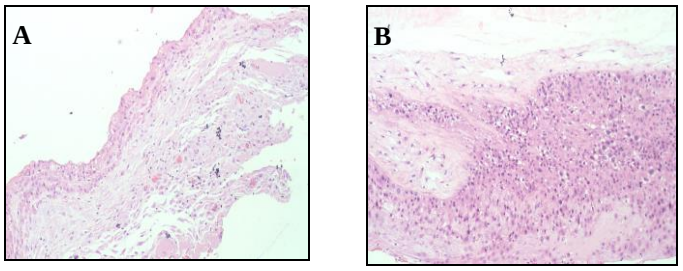
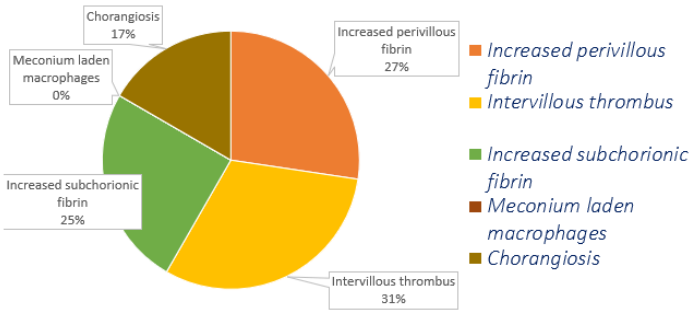




Figure 3. Membrane rolls with chorionitis (H&E; A. x 100; B x400).

Table 6. Miscellaneous pathology
(28 placentas in H. Adam Malik General Hospital Medan Feb-Aug 2021)



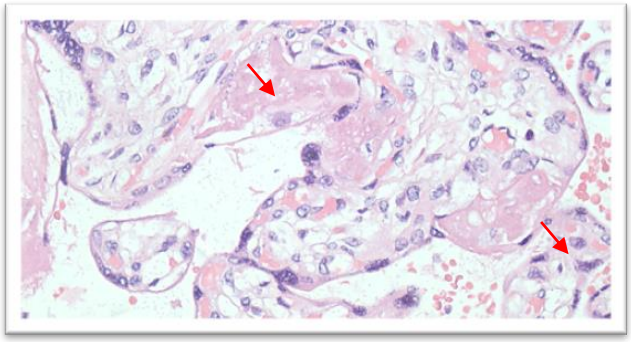



Figure 4. Section of placenta showing perivillous fibrin (H&E; x 400).

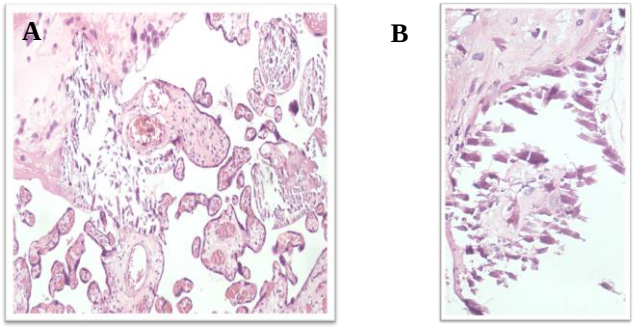



Figure 5. Villous stromal karryorhexis (H&E; A. x100; B. x 400).

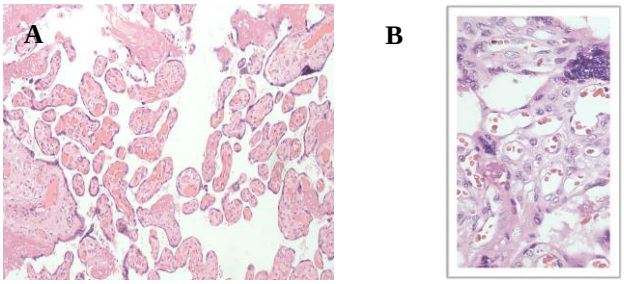



Figure 6. Fetal villi with chorangiosis (H&E; A. x 100; B. x400)

Table 7. Miscellaneous pathology
(28 placentas in H. Adam Malik General Hospital Medan Feb-Aug 2021)

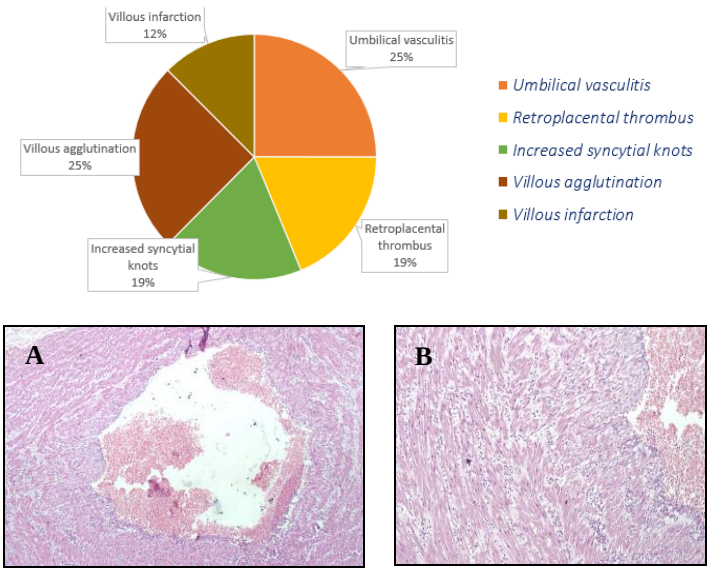



Figure 6. Umbilical vasculitis, the infiltrating polymorphs on vessel muscle (H&E; A. x 40; B. x100)

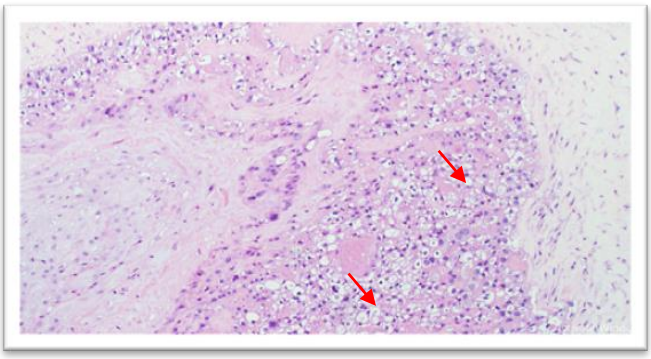


Figure 7. Macrophages diffusely spread (H&E; x 100).

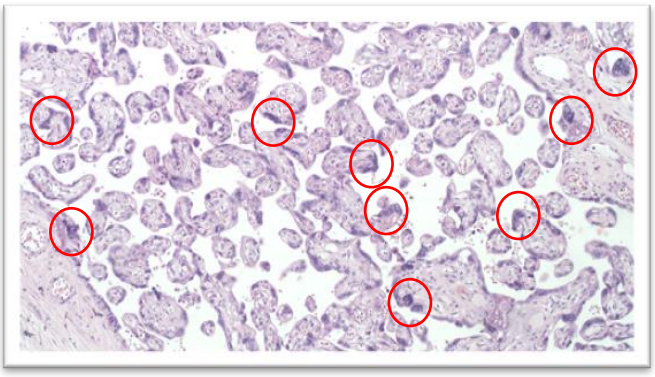


Figure 8. Pathological findings of increased syncytial knots (H&E stain; x 100)

## IV. DISCUSSION

SARS-CoV-2 gains access to cells in humans via angiotensin converting enzyme 2 (ACE-2). The more ACE-2 on the surface of the placental cells, especially in the syncytiotrophoblast, the potential for vertical transplacental transmission to the fetus will increase in pregnant women infected with COVID-19. Several studies have reported that although the placenta tested positive for SARS-CoV-2, very few newborns showed disease caused by the virus, so it is interesting to know more. The protective effect of the placenta is still a mystery, the possibility of the placenta being a barrier to viral infection and limiting the spread of the virus to the newborn. The detrimental role of COVID-19 in pregnancy is largely debated, although COVID-19 infection in pregnant women results in unfavorable pregnancy outcomes.[4] Research conducted by Robbins in 2012 reported that infection in the mother is not the same as infection in the placenta and viral infection in the placenta does not guarantee vertical intrauterine transmission to the fetus.[5] The placenta has an immunological reaction that blocks the entry of pathogens and maintains immune tolerance to fetal cells. It has been suggested that a possible key role in protecting the fetus and neonate against SARS-CoV-2 infection is the innate immune system.[6]

The number of samples with plasenta from mothers tested COVID-19 positive in this study were 28 samples, with a mean age of 29,46, where youngest age was 17 years and oldest age was 42 years. In this study, placental histopathologic findings

like maternal vascular malperfusion at most is decidual vasculopathy, excessive infarction, distal villous hypoplasia, accelerated villous maturation, the last one is old hemorrhage in membranes. There is several data from research results on placental pathology from pregnant women with SARS-CoV-2 infection. A recent study found fetal vascular malperfusion in the placenta with nonacute SARS-CoV-2 infection[7,8,9] and maternal vascular malperfusion.[7] Gulersen et al. in 2020 reported that placental histopathologic findings like maternal vascular malperfusion at most is excessive infarction and there was no statistically significant difference in maternal vascular malperfusion histologic characteristics between the 2 groups from placentas women after diagnosis of SARS-CoV-2 infection and gestational age matched historical controls.[9] Baergen and Heller have also recently reported placental findings from 20 cases of third-trimester maternal SARS-CoV-2 infection. They found incidences of maternal vascular malperfusion in 20% of case.[3] Boyraz et al. in 2022 have also recently reported placental findings showed maternal vascular malperfusion in 20,9% of case.[11] Maternal vascular malperfusion in the placenta of a mother infected with COVID-19 can cause significant clinical sequelae, for example, preterm delivery, growth retardation of the fetus, and fetal death. Maternal pulmonary hypoxia due to severe COVID-19 infection can result in uterine underperfusion and subsequent hypoxic-ischemic injury to the placenta.[12]

In this study, placental histopathologic findings like fetal vascular malperfusion at most is intramural fibrin deposition. Then successively villous stromal vascular karyorrhexis and stem vessel obliteration. Gulersen et al. in 2020 reported that placental histopathologic findings like fetal vascular malperfusion just only 6,2%.[9] Baergen and Heller have also recently reported placental findings from 20 cases of third-trimester maternal SARS-CoV-2 infection. They found incidences of low-grade fetal vascular malperfusion in 45% of case.[3] Boyraz et al. in 2022 have also recently reported placental findings showed fetal vascular malperfusion in 16.4% of case.[11] Sequelae after severe maternal COVID-19 infection in the form of an inflammatory response in the fetus, possibly related to endothelial or vascular wall damage, pathogenesis being evidence of vascular thrombosis in the fetal circulation.[13] A study conducted by Ernst in 2018 reported that patients with a history of COVID-19 during pregnancy may be at risk for significant placental pathologies including maternal vascular malperfusion and fetal vascular malperfusion, both of which are associated with increased perinatal morbidity.[14]

In this study, placental histopathologic findings like inflammatory lesions at most is chronic deciduitis and maternal response (chorionitis). Then successively fetal response (amnionitis) and chronic villitis. Gulersen et al. in 2020 reported that placental histopathologic findings like chorionitis (12,5%), amnionitis (12,5%) and chorangiosis (6,2%).[9] Boyraz et al. in 2022 have also recently reported placental findings showed inflammatory pathologic findings in 20.9% of case.[11]

In this study, placental histopathologic findings like miscellaneous pathology at most is intervillous thrombus. Then successively increased perivillous fibrin, increased subchorionic fibrin, umbilical vasculitis, villous agglutination, retroplacental thrombus, increased syncytial knots, chorangiosis_chorangioma and villous infarction. Gulersen et al. in 2020 reported that placental histopathologic findings like increased perivillous fibrin 12,5% and intervillous thrombus (37,5%).[9] Boyraz et al. in 2022 have also recently reported placental findings showed 11.9% infectious pathologic findings and 10.4% thrombotic findings.[11] Villous stromal-vascular karyorrhexis may result from damage or destruction of fetal endothelial cells in the villous stroma. Depending on the severity and nature of the obstruction, there may be a risk of fetal growth restriction, oligohydramnios, inconclusive fetal heart rate, and death.[15]

## V. CONCLUSION

A study was conducted on patients with maternal SARS-CoV-2 infection on placental pathology at Department of Anatomic Pathology, USU Medical Faculty and Anatomic Pathology Unit, H. Adam Malik Hospital Medan with following conclusions:

1. Limited conclusions can be drawn about the effect of maternal SARS-CoV-2 infection on placental pathology.
2. Based on the data in this study, we report general histopathological features, which include maternal vascular malperfusion, fetal vascular malperfusion, inflammation and thrombus in placentas with COVID-19 infection.
3. A prospective cohort study with a larger sample population with thorough placental examination is needed to understand the impact of SARS-CoV-2 on the placenta, pregnancy and possible fetal sequelae.

## VI. COMPETING INTERESTS

Author has no financial interests relevant to product or company described in this article.

## VI. ACKNOWLEDGMENT

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