*ORIGINAL ARTICLE*

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 – 9203

# Histopathological Features of Placentas from Mothers Infected with COVID-19 During Pregnancy

## Gebeliği Sürecinde COVID-19 Enfeksiyonu Geçiren Annelerin Plasentalarının Histopatolojik Özellikleri

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**ÖZ**

**Amaç:** Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) vücuda alındıktan sonra solunum sistemi başta olmak üzere birçok dokuda morfolojik değişikliklere neden olabilir. COVID-19'lu gebe bireylerde, SARS-CoV-2'nin dikey geçişi mümkün olabilir ve düşük, fetal malformasyonlar, fetal büyüme kısıtlaması veya ölü doğum gibi gebelik komplikasyonlarına neden olabilir. Bu çalışmada COVID-19'lu kadınların plasentalarında meydana gelen değişiklikler araştırılmıştır.
**Araçlar ve Yöntem:** Bu çalışmada gebeliğin herhangi bir döneminde COVID-19 tanısı alan 29 kadının plasentasının histopatolojik özellikleri değerlendirildi.
**Bulgular:** Çalışmaya dahil edilen kadınların yaşları 18 ile 40 arasında değişmekte olup, yaş ortalaması 30.3'tür. Bir hastanın doğum haftaları 32. hafta, sekiz hastanın doğum haftası 40. hafta, diğerleri ise 36 ve 39. haftalardı. Hiçbir hastada herhangi bir komorbidite yoktu. Histopatolojik incelemede kalsifikasyonlar, konjestif koryon villuslar, intervillöz kanamalar ve sinsityal düğümlerde artış sık görülen bulgulardı. 3 olguda fibromusküler stenoz, 2 olguda belirgin distal villöz hipoplazi gözlendi.
**Sonuç:** Plasenta, viral enfeksiyonların fetüse bulaşmasını önlemek için bariyer görevi gören çeşitli mekanizmalara sahiptir. Çalışmalar, COVID-19'lu gebe kadınlarda plasental patolojide, özellikle maternal vasküler malperfüzyon sıklığında bir artış olduğunu göstermiştir. Çalışma ayrıca hamilelik sırasında COVID-19 enfeksiyonu olan annelerin plasentasında fetal ve maternal vasküler malperfüzyon dahil olmak üzere plasental anormalliklerin meydana gelebileceğini gösterdi.

**Anahtar kelimeler:** COVID-19 pandemisi; gebelik komplikasyonları; plasenta

**ABSTRACT**

**Purpose:** After the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the body, it can cause morphological changes in various tissues, particularly those of the respiratory system. In pregnant individuals with COVID-19, vertical transmission of SARS-CoV-2 may occur and has been associated with pregnancy complications such as miscarriage, fetal malformations, fetal growth restriction, and stillbirth. This study aimed to investigate the histopathological changes observed in the placentas of women infected with COVID-19 during pregnancy.
**Materials and Methods:** In this study, the histopathological features of the placenta of 29 women with COVID-19 at any period of pregnancy were evaluated.
**Results:** The women included in the study ranged in age from 18 to 40 years, with a mean age of 30.3. The birth week of one patient was the 32nd week, eight patients was the 40th week, and the others were at 36 and 39 weeks. None of the patients had comorbidities. In histopathological examination, calcifications, congestive chorionic villi, intervillous hemorrhage and increase in syncytial knots were common findings. Fibromuscular stenosis was observed in 3 cases and marked distal villous hypoplasia in 2 cases.
**Conclusion:** The placenta possesses several mechanisms that act as barriers to prevent the transmission of viral infections to the fetus. Studies have demonstrated an increase in placental pathologies, particularly a higher frequency of maternal vascular malperfusion, in pregnant women with COVID-19. Moreover, these studies have shown that placental abnormalities, including both fetal and maternal vascular malperfusion, may occur in the placentas of mothers infected with COVID-19 during pregnancy.

**Keywords:** COVID-19 pandemic; placenta; pregnancy complications

Received: 22.01.2025; Accepted: 10.06.2025

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How to cite: Yeldir N, Sönmez Ünal G, Özer H. Histopathological features of placentas of mothers who have had COVID-19 infection during pregnancy. Ahi Evran Med J. 2025;9(3):317-322. DOI: 10.46332/aemj.1625301

## INTRODUCTION

The COVID-19 pandemic, which began in Wuhan, China on November 17, 2019, has had a global impact. After the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is ingested into the body, it can cause morphological changes in many tissues, especially the respiratory system. The virus causes fever, cough, myalgia, pharyngitis, diarrhea, pneumonia, acute respiratory distress syndrome, multisystem organ failure, cytokine storms and thrombotic events.[1,2]

While COVID-19's effects on the respiratory system are well documented, its impact on fetal development through placental changes remains unclear. Some viral species, such as rubella and herpes simplex virus, can cause congenital viral infections; however information on the vertical transmission of SARS-CoV-2 is limited, although there are case reports.[3] In pregnant women with COVID-19, the fetus can potentially be affected by the virus-infected placenta.

Since the beginning of the COVID-19 pandemic, pregnant women have been defined as a high-risk group. SARS-CoV-2 infection can cause poor fetal outcomes during pregnancy, including growth retardation, premature birth and death.[4]

The objective of this study was to examine the histopathological alterations observed in the placentas of pregnant women diagnosed with COVID-19.

## MATERIALS and METHODS

Approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (dated 20.10.2021 and numbered 2021-10/22).

The study was performed prospectively with 29 women who had COVID-19 infection at any period of their pregnancy and gave birth via cesarean section or vaginal delivery. The study included pregnant women who were hospitalized for delivery, regardless of their vaccination status or symptoms of COVID-19. The patients' data were evaluated for clinical presentation, timing of COVID-19 infection during pregnancy and placental histopathological features.

The demographic and clinical information of the patients was obtained from hospital the information system. Demographic and clinical information of pregnant women include ages, gestational ages (weeks), presence of active COVID-19 infection in delivery, vaccination status, gravidity, parity and comorbidities.

### Informed Consent

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

### Histopathological Evaluation

All placental specimens were prepared for microscopic examination at the Department of Pathology. For each placenta, two sections representing the periphery and center were examined. Two experienced pathologists performed all histopathological and morphological analyses. Analyses were performed by light microscopy of hematoxylin and eosin- stained sections. The placental tissue findings were defined according to the period of pregnancy of COVID-19.

## RESULTS

Twenty-nine pregnant women were included in the study. Their ages ranged from 18 to 40 years, with a mean of 28 years. The birth week of a patient was the 32nd week and the birth week of eight patients was the 40th week. Also the birth week of the others varied between 36th and 39th weeks. None of the patients had comorbidities.

Fourteen women were unvaccinated in this study. For the fifteen vaccinated patients, two patients have a single dose, two patient have three doses and the others have two doses. At the time of birth, three patients had an active covid infection period. Six patients had covid infection in the first trimester. Seven patients had covid infection in the second trimester. Seven patients had covid infection in the third trimester. The period in which six patients had infection is unknown.

Macrosomia was detected in one newborn. The mother of this baby was vaccinated, had a covid infection in the first trimester and gave birth in the 40th week. Additionally, intrauterine growth retardation was observed in two newborns. The mothers of these babies were vaccinated in the first trimester. Clinical and demographic information of pregnant women are summarized in Table 1.

**Table 1.** Clinical and demographic information of pregnant women in the study.

| Patient number | Mother's age | Week of birth | Vaccine status | Gravidity | Parity |
|---|---|---|---|---|---|
| 1 | 19 | 39 | None | 1 | 0 |
| 2 | 29 | 40 | Two doses | 3 | 2 |
| 3 | 29 | 40 | None | 1 | 0 |
| 4 | 25 | 40 | None | 4 | 3 |
| 5 | 43 | 36 | Two doses | 3 | 2 |
| 6 | 31 | 34 | None | 2 | 1 |
| 7* | 39 | 40 | None | 2 | 1 |
| 8 | 23 | 39 | Two doses | 2 | 1 |
| 9 | 27 | 39 | None | 1 | 0 |
| 10* | 23 | 32 | Two doses | 2 | 1 |
| 11* | 31 | 37 | None | 2 | 2 |
| 12 | 23 | 39 | None | 1 | 0 |
| 13 | 23 | 39 | None | 4 | 3 |
| 14 | 39 | 39 | None | 3 | 2 |
| 15 | 35 | 37 | Two doses | 2 | 1 |
| 16 | 27 | 40 | None | 4 | 3 |
| 17 | 28 | 39 | A dose | 2 | 1 |
| 18 | 32 | 28 | Two doses | 4 | 3 |
| 19 | 28 | 39 | None | 2 | 2 |
| 20 | 21 | 38 | Two doses | 2 | 1 |
| 21 | 35 | 37 | Two doses | 3 | 2 |
| 22 | 22 | 40 | Two doses | 1 | 0 |
| 23 | 27 | 39 | Two doses | 3 | 2 |
| 24 | 27 | 40 | None | 2 | 1 |
| 25 | 29 | 38 | Three doses | 4 | 3 |
| 26 | 25 | 38 | Two doses | 2 | 1 |
| 27 | 21 | 39 | Three doses | 2 | 1 |
| 28 | 30 | 40 | A dose | 2 | 1 |
| 29 | 18 | 39 | None | 1 | 0 |

*Pregnant women who gave birth with active infection.

Macroscopic examination of the placenta, revealed no findings on the cross-sectional surfaces. Placental weights were within normal limits. The umbilical cord contained 2 arteries and 1 vein.

On histopathological examination, the most common findings were calcification (19 cases), congestive chorionic villi (8 cases), and increase in syncytial knots (13 cases) (Figure 1). Histiocytic villitis (3 cases), infarct (2 cases) and retroplacental hemorrhage (1 case) were the least common findings. Other findings were perivillous fibrin deposition (9 cases) (Figure 2), intervillous hemorrhage (10 cases), distal villous hypoplasia (8 cases) (Figure 3), increase in Hofbauer cells (6 cases), and hydropic changes in villi (6 cases). In addition, fibromuscular stenosis was observed in 5 cases (Figure 4). Histopathological features and pathological findings about infants are summarized in Table 2.

## DISCUSSION

Coronaviruses are a family of viruses that can cause a variety of respiratory symptoms and serious complications.[5,6] Angiotensin-converting enzyme 2 (ACE2) is the primary receptor of SARS-CoV-2. Placental syncytiotrophoblasts, cytotrophoblasts, and endothelial cells highly express ACE2. The virus binds to ACE2 and enters the cells. The clinical outcomes of viruses are likely dependent on both direct cell damage and the host response. SARS-CoV-2 infections increase cytokines associated with T-helper (Th)1 and Th2 cells.[7]

**Table 2.** Histopathological findings of placentas and corresponding pathological conditions in infants, categorized by gestational age.

| The period of pregnancy of COVID-19 | Pathological findings in the infants | Histopathological features of the placentas |
|---|---|---|
| Delivery with active COVID-19 infection (3 cases) | No finding | Congestive chorionic villus (3 cases)<br>Perivillous fibrin deposition (2 cases)<br>Fibromuscular stenosis (1 case)<br>Intervillous hemorrhage (1 case)<br>Hydropic changes in villi (1 case)<br>Increase in Hofbauer cells (1 case) |
| First trimester (11 cases) | Macrosomia (1 case) | Calcifications (8 cases)<br>Increase in syncytial knots (4 cases) |
| | Intrauterine growth retardation (2 cases) | Distal villous hypoplasia (4 case) Intervillous hemorrhage (5 cases)<br>Congestive chorionic villus (3 cases)<br>Hydropic changes in villus (3 case)<br>Perivillous fibrin deposition (3 cases)<br>Histiocytic villitis (2 cases)<br>Increase in Hofbauer cells (2 cases)<br>Fibromuscular stenosis (2 cases) |
| Second and third trimester (15 cases) | No finding | Calcifications (11 cases)<br>Increase in syncytial knots (9 cases)<br>Congestive chorionic villus (5 cases)<br>Intervillous hemorrhage (4 cases)<br>Distal villous hypoplasia (4 cases) Perivillous fibrin deposition (4 cases)<br>Increase in Hofbauer cells (3 cases)<br>Fibromuscular stenosis (2 cases)<br>Infarct (2 cases)<br>Hydropic changes in villus (2 cases) Histiocytic villitis (1 case)<br>Retroplacental hemorrhage (1 case) |

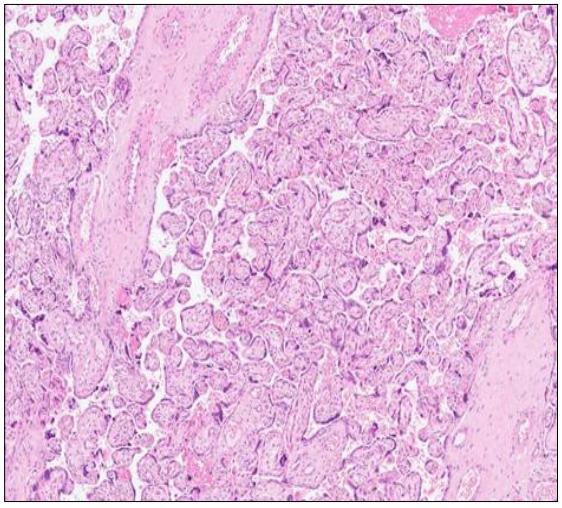

**Figure 1.** Increase in syncytial knots in a placenta of 39th week of gestation (HE x200).

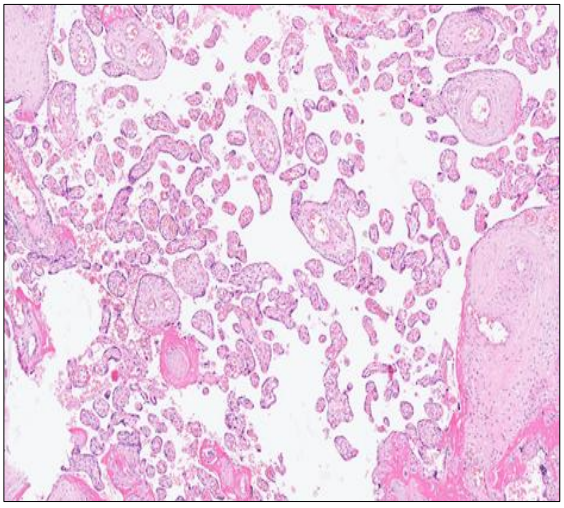

**Figure 3.** Distal villous hypoplasia in a placenta of 40th week of gestation (HE x200).

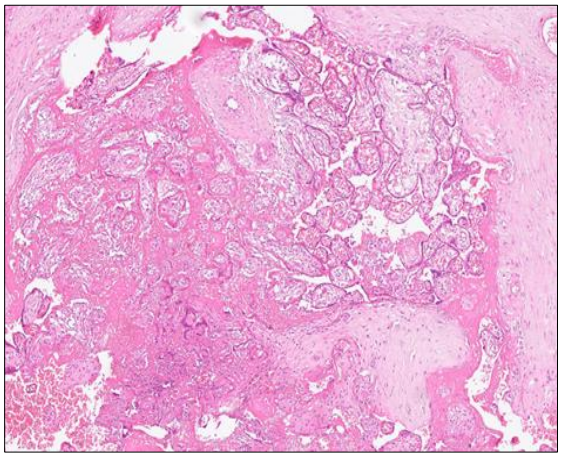

**Figure 2.** Massive fibrin deposition in a placenta of 38th week of gestation (HE x 200).

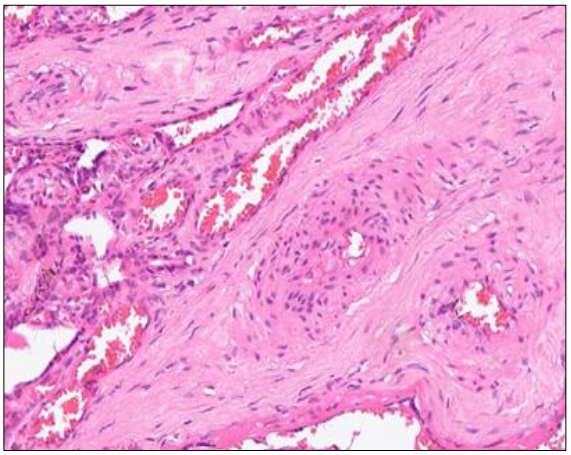

**Figure 4.** Fibromuscular stenosis in a placenta of 40th week of gestation (HE x200).

The placenta has several mechanisms that act as barriers to prevent the transmission of viral infections to the fetus.[8] Studies have shown an increase in placental pathology, especially the frequency of maternal vascular malperfusion, in pregnant women with COVID-19, but the effect of the timing and severity of infection on placental pathology is limited.[9]

One study found that, mural hypertrophy of the vessel wall in the placenta was a common finding in COVID-19 positive pregnant women.[10] In another study, the three most common findings in SARS-CoV-2 infected placentas were increase in fibrin deposition, villous trophoblast necrosis and chronic histiocytic intervillositis.[11] Chronic inflammatory placental disorders, such as villitis, chronic histiocytic intervillositis and massive perivillus fibrin deposition can cause adverse pregnancy outcomes by affecting the placental architecture.[12]

This was a prospective study involving 29 female patients with COVID-19 infection at any time during pregnancy. In this study, the most common findings were calcifications, increase in syncytial knots, and congestive chorionic villi.

The most common findings of placenta were congestive villus and perivillous fibrin deposition in women with active infection during delivery. None of them contained calcification. Some studies have reported that COVID-19 positive placentas show increased features of malperfusion such as microcalcifications, fibrin thrombi and syncytial knotting compared to COVID-19 negative placentas.[6]

Maternal and fetal developmental and malperfusion findings such as distal villous hypoplasia, perivillous fibrin deposition, intervillous hemorrhage, fibromuscular stenosis and villous infarction of varying severities were observed in the placental tissues.[13] In a case report, it was mentioned that the SARS-CoV-2 virus caused placental failure and fetal death with maternal-vertical transmission. It is reported that histology of the placenta showed villous trophoblast necrosis associated with histiocytic intervillocytes and massive perivillous fibrin deposition.[14]

In some studies, significantly different pathological results have been observed in placentas with confirmed COVID-19 positivity compared to the group with no evidence of infection. Especially, chronic histiocytic intervillositis is emphasized as a placental finding associated with COVID-19.[15] Histiocytic villitis was found in 3 cases in this study.

Studies about the protection of the vaccine against the mother or baby are limited. In a study, vaccination during pregnancy is found safety and effective in preventing maternal infection without increasing the risk of adverse neonatal and maternal outcomes.[16] Fourteen pregnant women were unvaccinated and fifteen patients were vaccinated in this study. One of patients with two dose vaccination had active infection in delivery.

According to the results of numerous studies, SARS-CoV-2 infection during pregnancy necessitates hospitalization, intensive care, and mechanical ventilation.[17] Some studies have shown that COVID-19 infection during pregnancy is associated with preterm birth and maternal death. Maternal and fetal deaths were not found in this study group. There was no preterm birth, as well. Intrauterine growth retardation was detected in the babies of two mothers who had COVID-19 in the first trimester. There are also studies indicating that COVID-19 infection during pregnancy can result in severe growth retardation in newborns.[18]

Management of pregnant women with COVID-19 infection largely follows the standard approach for pregnant women without the infection. In delivery planning, gestational age, fetal maturity, maternal oxygenation status, and the potential impact of maternal hypoxemia on the fetus should be assessed. Delivery should be considered in patients experiencing hypoxemia or when maternal clinical deterioration occurs due to severe infection, particularly at or beyond 32 weeks of gestation.

**Study Limitations**

The limitation of the study is that the sample size is not large. In this study, the common findings of placental tissues can not specific for COVID-19 infection and these findings were found in many disorders. We have data that similar to studies performed in a larger number of cases.

## Conclusion

It is believed that the SARS-CoV-2 virus can cause pregnancy complications such as fetal malformations, fetal growth retardation and stillbirth. Placental abnormalities including fetal and maternal vascular malperfusion have been reported despite negative SARS-CoV-2 tests in infants of mothers with COVID-19 infection during pregnancy. According to this study, COVID-19 infection can cause significant histopathological findings in placental tissues.

## Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

## Acknowledgements

The study was presented as a poster presentation in the best posters session at the 34th European Congress of Pathology.

## Ethics Committee Permission

Approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (dated 20.10.2021 and numbered 2021-10/22).

## Authors' Contributions

Concept/Design: NY, GSÜ, HÖ. Data Collection and/or Processing: NY, GSÜ. Data analysis and interpretation: NY, GSÜ, HÖ. Literature Search: NY, GSÜ, HÖ. Drafting manuscript: NY, GSÜ. Critical revision of manuscript: NY, HÖ. Supervısor: NY, GSÜ, HÖ.

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