Available online on 15.08.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Histopathological Changes in the Placentas of Pregnant Women with COVID-19

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Article Info:

Article History:

Received 13 May 2025
Reviewed 24 June 2025
Accepted 17 July 2025
Published 15 August 2025

Cite this article as:

Özdemir Başaran S, Kaplan Ö, Aşır F, Akkuş M, Ağaçayak E, Histopathological Changes in the Placentas of Pregnant Women with COVID-19, Journal of Drug Delivery and Therapeutics. 2025; 15(8):34-37 *DOI: http://dx.doi.org/10.22270/jddt.v15i8.7287*

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Abstract

Objective: This study aimed to investigate the placental histopathologic structure in placentas of COVID-19 pregnant patients.

Materials and Methods: In our study, small pieces of placentas of 20 pregnant women diagnosed with COVID-19 and 20 normal pregnant women admitted to Dicle University Faculty of Medicine, Department of Obstetrics and Gynecology were obtained for histologic follow-up. Placenta samples were stained with hematoxylin and eosin and examined under light microscopy.

Results: Placentas of the control group showed normal histologic structure. In the placenta samples of the patients belonging to the COVID-19 group, increased apoptotic process with pyknotic changes in the nuclei of decidua cells was observed. Fibrinoid tissue areas were significantly increased and syncytial bridges were enlarged in chorionic villi. In the area where the root villi were located, the membrane structure was disrupted with excessive thinning of the basement membrane and the vessels were highly dilated and congested. In the intervillous area, there were abundant free scattered erythrocytes, leukocyte invasion and hyalinized areas in the villous area.

Conclusion: As a result of the histopathological changes observed in the placental tissues of the COVID-19 group in our study, we concluded that COVID-19 induces degenerative changes in placental structure.

Keywords: COVID-19, placenta, histopathology

INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, emerged in November 2019 with pneumonia cases in Wuhan, China. It spread rapidly across the world in 2020 and was declared a pandemic by the World Health Organization (WHO) in March 2020[1]. SARS-CoV is highly pathogenic and lethal, causing severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure and death [2]. Angiotensin-converting enzyme 2 (ACE2) is the undisputed receptor for cellular entry of SARS-CoV-2 and studies have shown strong and widespread ACE2 receptors in cytotrophoblast, syncytiotrophoblast cells in placental villi as well as in extravillous trophoblasts [3]. However, since congenital transmission is a rare event and not all infected pregnant women have poor obstetric and neonatal outcomes, the possibility of fetal danger due to COVID-19 in the mother is still debated.

During this pandemic, there was limited scientific information on the impact of COVID-19 on pregnant women [4]. Recent studies have reported that severe SARS-CoV-2 infection may lead to an increased risk of maternal death and maternal morbidity [5]. Pregnant women with SARS-CoV-2 infection were found to have higher rates of preterm delivery and caesarean section compared to healthy pregnant women [6]. Pregnant women are considered a high-risk group due to the maternal and neonatal effects of COVID-19 that may occur both prenatally and postnatally. Vertical transmission of SARS-CoV-2 has been convincingly reported in many case reports and series; therefore, placental pathology has become the main area of interest [7].

In our study, placental histopathologic structures in placentas of COVID-19 pregnant patients were examined by histochemical techniques. Through this study, the effects of COVID-19 disease on the placenta were structurally analyzed.

MATERIALS AND METHODS

Project Design

This study was authorized by Dicle University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee with protocol number 492 and date 24.11.2021. This study was supported by Dicle University Research Projects Unit (DUBAP) with the

Project number (TIP. 22.006).The placentas used as material in the study were obtained from patients hospitalized in the Gynecology and Obstetrics Clinic of Dicle University Faculty of Medicine. Forty pregnant patients (18-49 years old), including 20 controls and 20 patients diagnosed with COVID-19, were included in the study. Patients with symptoms of cough, sore throat, fever and breathing difficulties and a positive COVID-19 RT-PCR test were accepted for the study. Tissue follow-up and histologic evaluation of the study were performed at Dicle University Faculty of Medicine Histology and Embryology Research Laboratory.

Histological Tissue Processing

Placental tissue samples were obtained as small sections from both maternal and fetal regions and processed using standard histological techniques. Initially, the samples were fixed in 10% neutral-buffered formalin for 24 hours at room temperature. Following fixation, the tissues were then kept overnight under running tap water to remove formalin and dehydrated in increasing alcohol series (50%, 70%, 80%, 90%, 96% and absolute ethanol). For transparency, they were kept in xylene for 2x30 minutes and the alcohol was removed. Paraffin infiltration was conducted in an oven at 58°C for 3x45 minutes each.The paraffin-embedded tissues were then blocked and sectioned at a thickness of 5–6 µm using a rotary microtome (Leica RM2265, Wetzlar, Germany). The sections were mounted on glass slides and stained with Hematoxylin and Eosin (HE) for histopathological examination [8].

Hemotoxylene Eosin Staining

Placental tissue sections taken from paraffin blocks with a microtome were placed in bain-marie (37°C). The sections were kept in an oven at 58-62°C for 6-8 hours to remove the excess paraffin remaining on the positively charged slide. The sections were then deparaffinized in xylene (3x15 minutes). To remove xylene, the sections were passed through decreasing alcohol series (100%, 96%, 90%, 70%, 50% ethyl alcohol) for 10 minutes each and brought to distilled water step and left for 5 minutes. Sections were stained with hematoxylin and eosin. After staining, the sections were rapidly immersed in increasing alcohol series (80%, 90%, 96% ethyl alcohol series) and kept in absolute ethanol for 2 minutes. Finally, the sections were kept in xylene for 3x15 minutes and Entellan was dripped on the tissue and covered with a coverslip. The sections were evaluated and visualized in Zeiss Imager A2 photomicroscope [9].

RESULTS

Hematoxylin-Eosin staining findings

Figure 1 presents the histological section of the placenta from the control group. The decidual cells in the maternal region are polygonal in shape, with chromatin-rich nuclei located centrally.Although there were fibrinoid structures around, there was not much dilatation of the vessels in general. In the root villi of chorionic villi, regular syncytial formations, very few syncytial bridges and syncytial nodes were detected. While connective tissue cells were diffuse and solitary in the normal area, especially collagenized structures were found to have a smooth course (Figure 1a). In the area where the umbilical cord arteries and veins continued from the maternal region, especially the lumens of the arteries were regular and there was no change in any media layer. Syncytial cells and cytotrophoblast cells were regular in the root villi. There was no hemorrhage in the intervillous areas, but there were few and thin syncytial bridges and few syncytial nodes. Intravillous fetal blood vessels were also regular (Figure 1b).

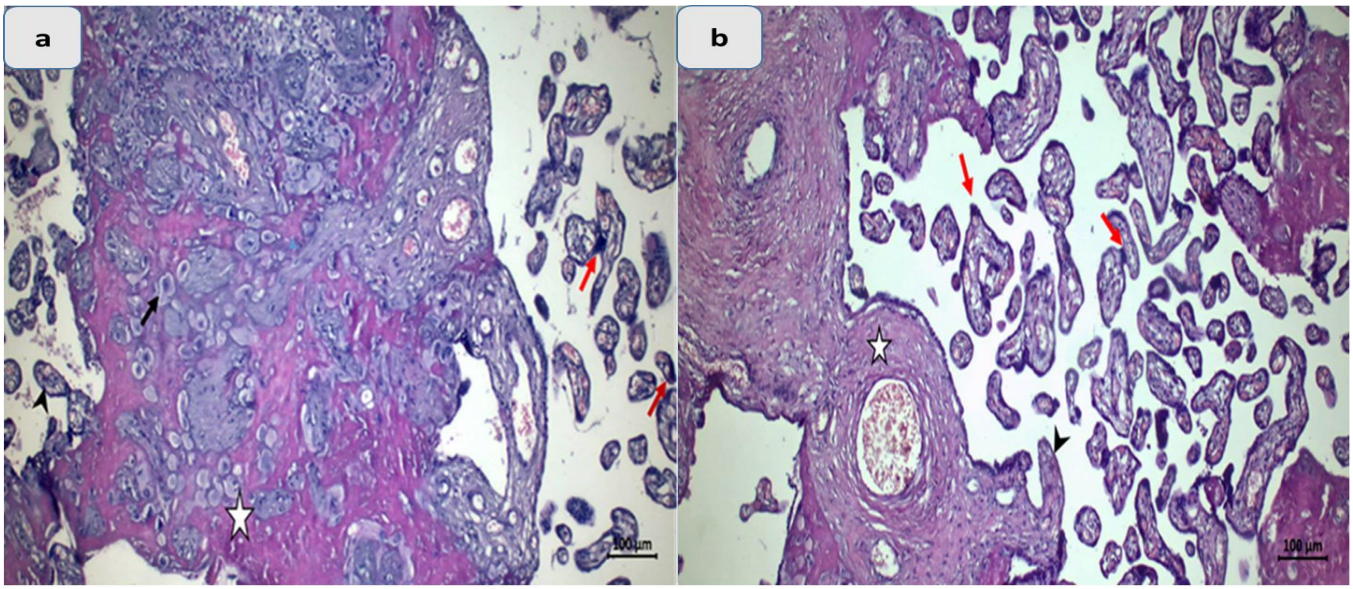

Figure 1 a): Control group:Normal looking polygonal shaped, chromatin dense decidua cells (black arrow), regular root villi (black arrow head), few syncytial nodes and bridges (red arrow), few fibrinoid areas (asterisk). b). Control group : The artery (black star) with a smooth media layer and lumen, regular syncytio-cytotrophoblast cells in the root villi (black arrowhead), few and thin syncytial bridges and nodes (red arrow) were observed. Hematoxylin Eosin, Bar: 100 µm, Magnification: 10X

In placental sections from the COVID-19 group, decidual cells in the maternal region exhibited pyknotic nuclei, indicative of enhanced apoptotic activity.Fibrinoid tissue areas were significantly increased. Especially hyalinized areas were detected in the area where the root villi were located towards the syncytial region. Again, hemorrhages and dilatations were detected in the blood vessels within the very prominent villus structures. While fibrinoid tissue formations were observed in the total intervillous area, abundant erythrocyte and leukocyte accumulation was observed in the intervillous areas (Figure 2a). In the umbilical cord vessels continuing from the maternal region, excessive dilatation and thinning of the wall structure, especially deterioration of the tunica media layer and hyalinized areas were detected. In the area where the root villi were located, excessive thinning of the basement membrane and disruption of its structural integrity were observed. Syncytial bridges were found to be enlarged, especially in the chorionic villi, with an increase in fibrinoid tissue in places. There was an increase in hyalinized tissue in the villi area and fibrosis was remarkable. It was prominent that the syncisial structure was completely disrupted (Figure 2b).

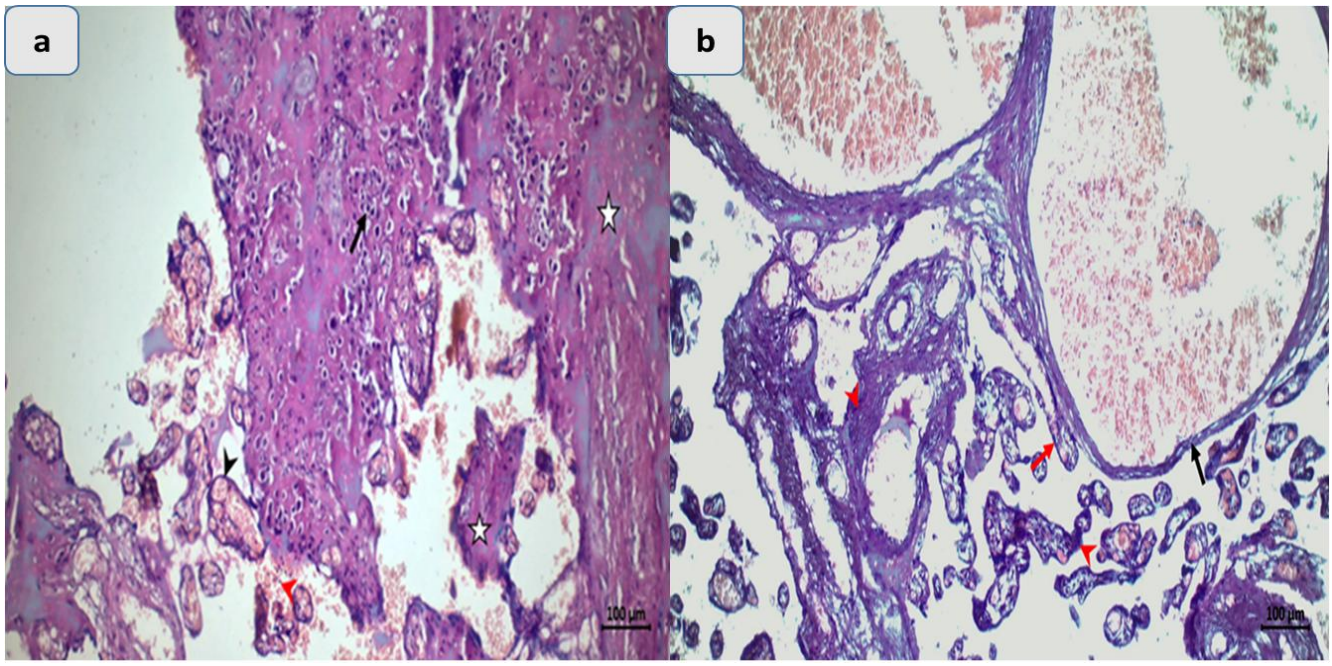

Figure 2 a): COVID-19 group: Decidua cells with picnotic nuclei (black arrow), areas of increased fibrinoid tissue (asterisk), dilatation and hemorrhage in intravillous vessels (black arrowhead), intervillous erythrocyte and leukocyte accumulation (red arrowhead). b).COVID-19 group: Extreme dilatation and thinning of the wall structure in vessels (black arrow), thinning of the basement membrane in villi (red arrow), increased fibrinoid tissue and enlargement of syncytial bridges (arrowhead). Hematoxylin Eosin, Bar: 100 µm, Magnification: 10X

DISCUSSION

SARS-CoV-2 is the etiological agent that caused the disease identified as COVID-19, which emerged towards the end of 2019. This virus is etiologically similar to the previously known severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which cause respiratory and gastrointestinal infections in humans. SARS-CoV-2, like the other two viruses, is highly pathogenic and can cause respiratory illnesses of varying severity, ranging from asymptomatic infections to mild and severe pneumonia, as well as acute respiratory distress syndrome (ARDS). With the advancing pandemic process, it has been seen that COVID-19 is not only a respiratory disease, but can affect many organ systems, including the placenta, and even result in death [10]. In a systematic review of pregnant women with COVID-19, it was reported that some mothers with severe pneumonia required intensive care, and the same study reported cases of abortion, maternal death, intrauterine and neonatal fetal death[2] . A study has shown that SARS-CoV-2 is vertically transmitted in humans and fetal vascular malperfusion (FVM) in the form of thrombotic vasculopathy has also been reported[11] . In a case-control study conducted on the placentas of SARS-CoV-2 positive mothers, an increased incidence of fibrin deposition, microcalcifications, syncytial nodes, small fibrotic villi, and villous agglutination was observed [12] . Shanes et al. [13] observed one intrauterine death in the second trimester and 15 live births in the third trimester in their study on 16 placentas taken from SARS-CoV-2 positive mothers. Histopathological changes consistent with characteristic findings such as intervillous thrombus formation and decidual arteriopathy were observed microscopically. They showed that fibrinoid necrosis, villous infarcts, villous agglutination, edematous villi and retroplacental hematoma occurred in the maternal placenta of fetal intrauterine death.

In our study, in the COVID- 19 placenta section taken from the maternal region, it was observed that the nuclei

of the decidua cells had a pyknotic appearance and the apoptotic process increased, and the areas of fibrinoid tissue increased significantly. Towards the syncytial region, hyalinized areas in the root villi and abundant erythrocyte and leukocyte accumulation in the intervillous areas were observed. In the umbilical cord vessels continuing from the maternal region, excessive dilatation and thinning of the wall structure, especially deterioration of the tunica media layer and hyalinized areas were detected. In the area where the root villi were located, thinning of the basement membrane and loss of structural integrity were observed, resulting in increased inflammation and syncytial degenerations and induced trophoblastic invasion.

CONCLUSION

In conclusion, COVID-19 infection during pregnancy caused significant histopathological changes in placental tissue, particularly fetal and maternal vascular malformations, impaired trophoblastic invasion, and decidual degeneration. Our study highlights the degenerative effect of SARS-CoV-2 on placental function.

Acknowledgement: This study is a part of the medical specialty thesis of Süreyya Özdemir Başaran, from Dicle University, Department of Histology and Embryology.

Funding: This study was funded by Dicle University Scientific Research Platform (DÜBAP, project no: TIP.22.006).

Ethical approval: This study was initiated with the approval of the Ethics Committee of Dicle University Faculty of Medicine dated 24.11.2021 and numbered 492)

Conflict of Interest: All authors declare there is no conflict of interest.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Informed Consent Statement: Not applicable.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

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