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Comparative study of pathomorphological changes in uterus and placenta during pregnancy with positive Omicron and Delta SARS-CoV-2 variants

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ABSTRACT: **In recent years, numerous studies have been conducted to examine the effects of COVID-19 on pregnancy; however, the pathomorphological changes in the uterus and placenta during this infection remain under-researched. This study aimed to evaluate pathomorphological changes in the uterus and placenta of pregnant women with positive COVID-19 results compared to a non-infected control group. A prospective analytical study including 48 pregnant women tested positive for COVID-19 (24 cases with Delta and 24 Omicron variants) and 42 pregnant women in the control group was conducted. Placental and uterine samples were analyzed using standard histological methods. Results indicated that pregnant women with COVID-19 showed a significant increase in the frequency of retroplacental hematomas, villous hypoplasia, vascular ectasia, and other histopathological changes in the uterus and placenta, especially in women tested positive for Delta variant. This study underscores that Delta SARS-CoV-2 variant is associated with marked pathological changes in the placenta and uterus, highlighting the need for careful clinical management in such pregnancies.**

KEYWORDS: **COVID-19, Delta (B.1.617.2) variant, Omicron (B.1.1.529), pathomorphology, placenta, pregnancy, SARS-CoV-2, uterus.**

INTRODUCTION

The coronavirus infection caused by the SARS-CoV-2 virus represents a global issue that significantly impacts various aspects of healthcare. In the context of pregnancy, COVID-19 raises particular concerns due to the potential health risks to both mother and fetus [1-3].

It is known that the placenta plays a key role in ensuring the normal development of the fetus by performing functions related to gas exchange, nutrition, excretion, and immune protection [4]. Histopathological examination of placental tissue and the maternal uterus can provide essential information about the health of both the mother and the newborn, as well as offer insights into the pathophysiological characteristics of the infectious process in both mother and fetus [5, 6].

Changes in the structure and function of the placenta can lead to various pregnancy complications, such as uteroplacental insufficiency, fetal growth restriction, and preeclampsia [5-7]. In the context of COVID-19, pathomorphological changes in the placenta and uterus may exacerbate these complications, highlighting the need for their detailed study.

Research has shown that viral and bacterial infections damage the placenta and fetus during the first and second trimesters of pregnancy, with disruptions in placental permeability, caused by the direct impact of inflammatory mediators, playing an important role [8-11].

COVID-19, caused by the SARS-CoV-2 (the severe acute respiratory syndrome coronavirus 2) virus, has gone through several stages of evolution, resulting in the emergence of various variants and strains. The study of the impact of various SARS-CoV-2 variants on pregnancy is a crucial task in modern medicine, considering their potential effects on maternal health and pregnancy outcomes [12, 13]. Currently, special attention is focused on virus variants such as the Delta (B.1.617.2) and Omicron (B.1.1.529) variants of SARS-CoV-2, which have become predominant in the population and significantly affect the incidence and spread of infection.

This study aimed to evaluate pathomorphological changes in the uterus and placenta of pregnant women with positive COVID-19 results compared to a non-infected control group.

MATERIALS AND METHODS

A prospective analytical study was conducted at the Republican Specialized Hospital Zangiota-1 (Tashkent, Uzbekistan). At our center, all pregnant women requiring hospitalization undergo testing for the novel coronavirus through nasopharyngeal reverse-transcription PCR (NP-RTPCR).

The study included pregnant women with a positive test for SARS-CoV-2 infection who were treated in the Zangiota-1 Maternity Complex. The COVID-19 group was divided into two subgroups: one with 24 cases of the Delta variant and the other with 24 cases of the Omicron variant. Pregnant women with pre-existing diagnoses of uteroplacental insufficiency, fetal growth restriction, hypertensive pregnancy disorders, or diabetes were excluded from the study. A total of 48 pregnant women with a positive SARS-CoV-2 test (24 cases of the Delta variant and 24 cases of the Omicron variant) and 42 women from the control group matched by age and gestational age were included in the study. The control group, consisting of 42 cases, included singleton pregnancies with negative SARS-CoV-2 results, matched by maternal and gestational age, occurring within the same timeframe. The study analyzed macro- and micro-preparations of the uterus and postpartum placenta of pregnant women.

Pathology and light microscopy

All biomaterials were fixed in 10% neutral buffered formalin and dehydrated by ethanol gradient for histopathological examination. Following fixation, paraffin sections (5-µm thick slices) were stained with hematoxylin and eosin, and light-optic microphotographs were taken using a "DN-300M" microscope with a digital camera and saved on computer using Microsoft Windows 10 Pro software.

The samples were photographed in different directions in 20 µm near the optic disc. Tissue samples were carefully examined by the expert pathologist in a blind and unbiased manner. Predefined criteria based on Amsterdam protocols were used to assess results, focusing on fetal vascular malperfusion and other related indicators [13, 14]. Standard histological methods were applied to evaluate the placental micropreparations [15].

Statistical analysis

A Duncan's multiple comparison tests has been performed to compare groups on all parameters, and we also analyzed the effect of COVID-19 with a one-way analysis of variance (ANOVA). The Kruskal–Wallis nonparametric test was used to compare histopathological parameters among the groups, and the Mann–Whitney U test was used to compare pairs of groups. All analyses were performed in SPSS 13.0.

Ethical approval

The review board and ethics committee of Republican Specialized Hospital Zangiota-1 approved the study protocol and informed consents were taken from all the participants.

RESULTS

This study aimed to analyze the pathomorphological changes in the uterus and placenta in pregnant women who have had COVID-19. The focus is on a comparative analysis of changes among patients with different SARS-CoV-2 variants (Omicron and Delta strains) and a control group without COVID-19. The mean age and gestational age do not significantly differ between the COVID-19 groups (Omicron and Delta strains) and the control group without COVID-19 ($P>0.05$). This suggests that age and gestational characteristics are not factors affecting the likelihood of pregnancy pathology development against the background of COVID-19.

There are no statistically significant differences in gravidity (number of pregnancies) and parity (number of births) distribution between the COVID-19 groups (Omicron and Delta strains) and the control group. This indicates a similarity in reproductive history between pregnant women with and without COVID-19. The proportions of first, second, third, and subsequent pregnancies among the COVID-19 groups (Omicron and Delta strains) and the control group also do not differ significantly ($P>0.05$), suggesting that previous pregnancy history is not associated with an increased risk of developing COVID-19 in pregnant women with uteroplacental insufficiency.

In the COVID-19 (Omicron and Delta) groups, similar percentages of women had no risk factors, with no statistically significant differences from the control group. Amniotic fluid leakage was absent in the COVID-19 groups but present in 11.9% of the control group ($P=0.021$). Fever history was more common in COVID-19 groups

than in the control group (P=0.006), while anemia and antepartum bleeding showed no significant differences (Table 1). Vaginal delivery was less frequent in COVID-19 groups, with more cesarean sections (P<0.001). Apgar scores were lower in COVID-19 groups, and although live births were slightly fewer (Table 2).

In the control group (n=42), the placenta macroscopically presented as follows: the fetal surface was smooth, grayish-blue in color, with moderate venous distention; the maternal surface of the placenta was uneven, soft in consistency, dark reddish-brown in color, with areas of hemorrhage (Figure 1).

Table 1. The presence of independent risk factors for uteroplacental insufficiency

Risk Factor	COVID-19 (Omicron, n=24)	COVID-19 (Delta, n=24)	Control (n=42)	*P* value
No, n (%)	14 (58.3%)	13 (54.2%)	27 (64.3%)	0.618
Yes, n (%)	10 (41.7%)	11 (45.8%)	15 (35.7%)	
Antepartum amniotic fluid leakage, n (%)	0	0	5 (11.9%)	0.021
Antepartum hemorrhage, n (%)	2 (8.3%)	1 (4.2%)	5 (11.9%)	0.69
History of fever, n (%)	7 (29.2%)	9 (37.5%)	3 (7.1%)	0.006
Chronic respiratory symptoms, n (%)	0	0	0	–
Anemia, n (%)	7 (29.2%)	9 (37.5%)	11 (26.2%)	0.787

Table 2. Perinatal outcomes in study groups

	COVID-19 (Omicron, n=24)	COVID-19 (Delta, n=24)	Control (n=42)	*P* value
Delivery method				
Vaginal birth, n (%)	8 (33.3%)	6 (25.0%)	35 (83.3%)	<0.001
Cesarean section, n (%)	16 (66.7%)	18 (75.0%)	7 (16.7%)	
Amniotic fluid color				
Blood stained, n (%)	1 (4.2%)	1 (4.2%)	2 (4.8%)	0.152
Clear, n (%)	18 (75.0%)	17 (70.8%)	31 (73.8%)	0.78
Meconium stained, n (%)	5 (20.8%)	6 (25.0%)	9 (21.4%)	0.381
Neonatal Apgar score (at 5 min)				
0-2, n (%)	0	0	0	--
3-4, n (%)	6 (25.0%)	7 (29.2%)	9 (21.4%)	0.188
5-6, n (%)	9 (37.5%)	10 (41.7%)	11 (26.2%)	0.431
7-10, n (%)	9 (37.5%)	7 (29.2%)	22 (52.4%)	0.045
Labor outcome				
Live birth, n (%)	19 (79.2%)	20 (83.3%)	37 (88.1%)	0.324
Still birth, n (%)	5 (20.8%)	4 (16.7%)	5 (11.9%)	

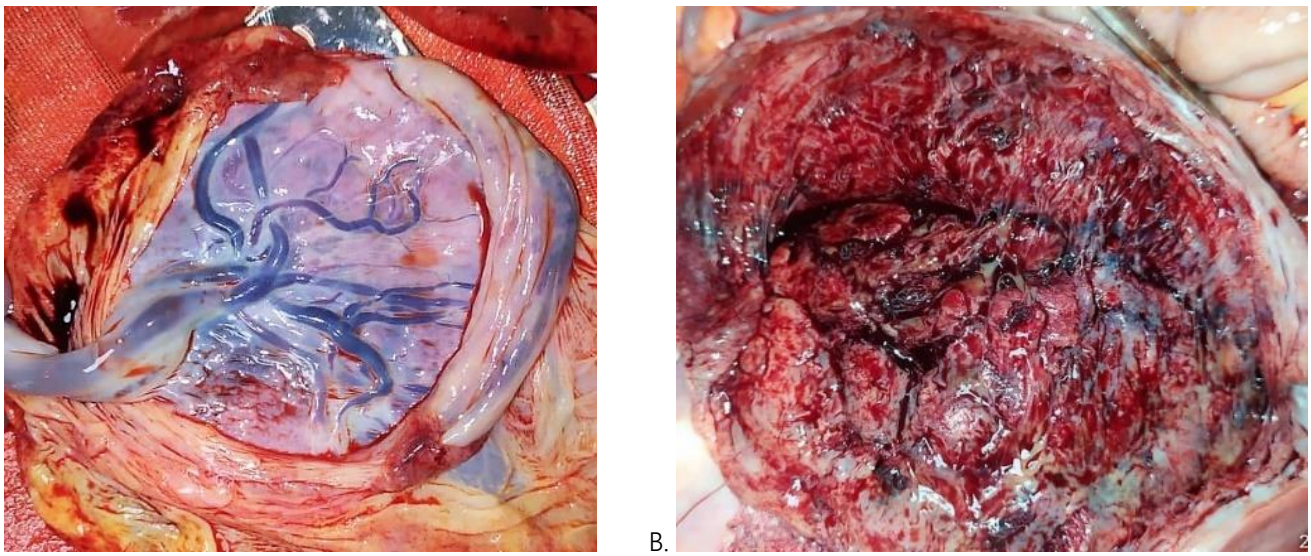


Figure 1. Macroscopic view of the placenta in the control group. A: Smooth fetal surface, grayish-blue in color with moderate vein distension. B. Maternal surface of the placenta is uneven, soft in consistency, and dark reddish-brown in color with areas of hemorrhage.

The placenta of women in the COVID-19 group

The placenta of women in the COVID-19 group (n=48) showed the following macroscopic features:

- The placentas were intact, with a smooth fetal surface, bluish-gray in color, and markedly distended and swollen veins.
- The maternal surface of the placenta exhibited moderate to pronounced hemorrhages, dark reddish-brown in color, with an uneven surface and a soft consistency (Figure 2).

Within the COVID-19 group, no macroscopic differences were found between Omicron and Delta variants. However, pathomorphological analysis showed significantly higher rates of maternal vascular malperfusion signs in SARS-CoV-2-positive pregnancies. Retroplacental hematomas (29.2% vs. 4.8%, P=0.002) and accelerated villous maturation (27.1% vs. 4.8%, P=0.005) were notably more frequent in the COVID-19 group compared to the control. Villous infarcts, though more common in COVID-19 cases, did not reach statistical significance (Table 3).

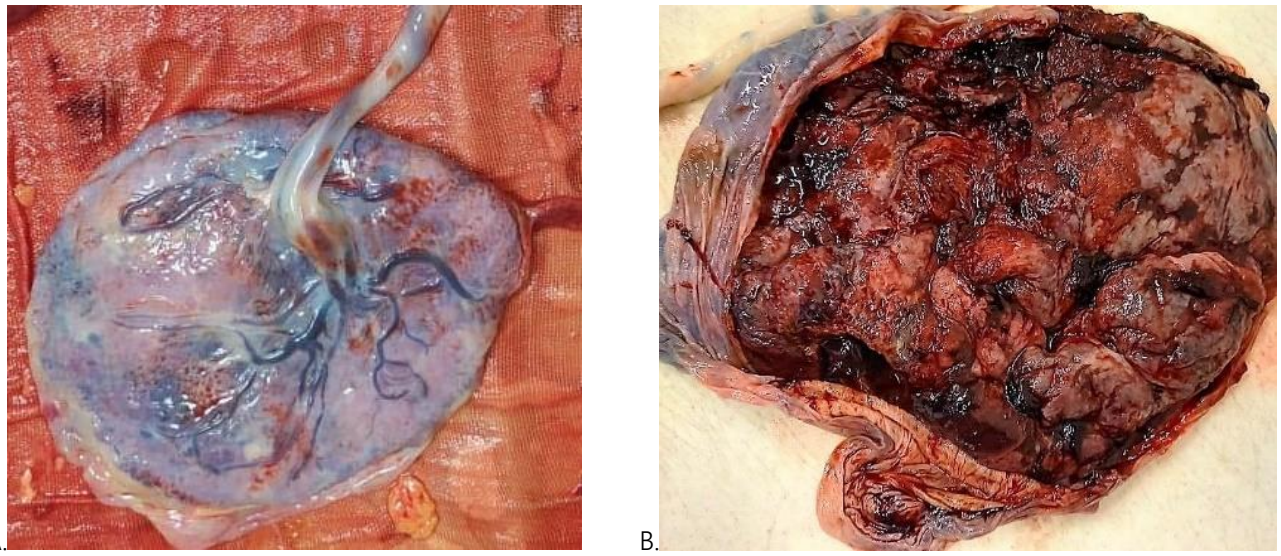


Figure 2. Macroscopic view of the placenta in the COVID-19 group. A: Placenta with intact structure, smooth fetal surface, bluish-gray in color, with veins highly distended and significantly edematous. B: Maternal surface of the placenta with moderate to pronounced hemorrhages, dark reddish-brown in color, uneven surface, and soft consistency.

Table 3. Histopathological changes in study groups

Histopathological changes	COVID-19 (n=48)	Control (n=42)	P value	Relative Risk (95% CI)
Villous infarctions	15 (31.3%)	9 (21.4%)	0.345	1,67 (0.64–4.34)
Retroplacental hematomas	14 (29.2%)	2 (4.8%)	0.002	8,24 (1.75–38.82)
Accelerated villous maturation	13 (27.1%)	2 (4.8%)	0.005	7,43 (1.57–35.22)
Villous hypoplasia	19 (39.6%)	5 (11.9%)	0.004	4,85 (1.62–14.54)
Acute atherosis/fibrinoid necrosis	7 (14.6%)	0 (0.0%)	0.013	–
Hyperplasia of the arteriolar walls of the basal lamina	4 (8.3%)	0	0.12	–
Thrombosis of the basal vessels of the decidua	4 (8.3%)	0	0.12	–
Hypertrophy of the membranous arterioles	28 (58.3%)	5 (11.9%)	<0.001	10.36 (3.46–31.00)
Dilated vessels	13 (27.1%)	0	<0.001	–
Preservation of endovascular trophoblast in the vessel walls	7 (14.6%)	0	0.013	–

Villous hypoplasia was more common among women with COVID-19 (39.6%) compared to the control group (11.9%) (P=0.004). Acute atherosis/fibrinoid necrosis was found in 14.6% of women with COVID-19 and was absent in the control group, showing a statistically significant difference (P=0.013). Hyperplasia of basal plate arteriolar walls and thrombosis of basal decidual vessels were observed in 8.3% of women with COVID-19 but were not present in the control group, though this difference was not statistically significant (P=0.120). Hypertrophy of membranous arterioles was the most common damage among women with COVID-19 (58.3%) compared to 11.9% in the control group (P<0.001). Dilated vessels were observed in 27.1% of women with COVID-19, while absent in the control group (P<0.001). Persistence of endovascular trophoblast in vessel walls was found in 14.6% of women with COVID-19, also absent in the control group, showing statistical significance (P=0.013) (Table 3).

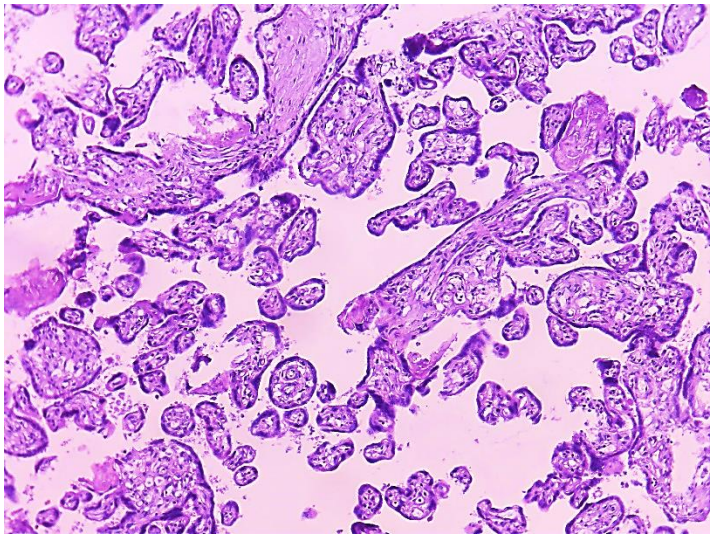


Figure 3. Placental tissue. Decidual tissue with moderate hyperplasia and mild expansion of the intervillous space. Control group.

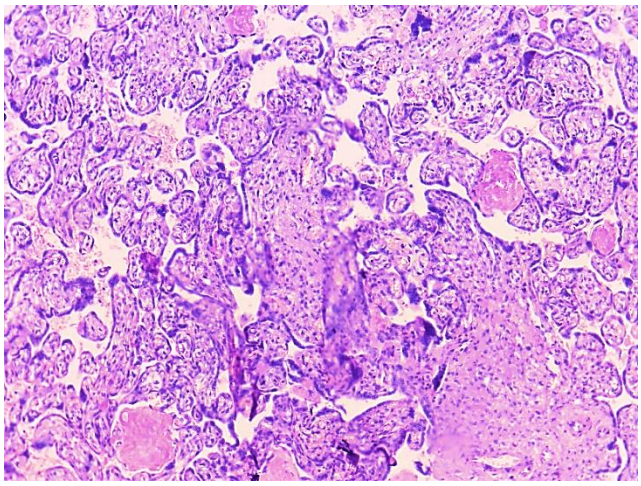


Figure 4. Placental tissue. Moderate proliferation (hyperplasia) of terminal villi and slight clusters of erythrocytes in the intervillous space. Control group.

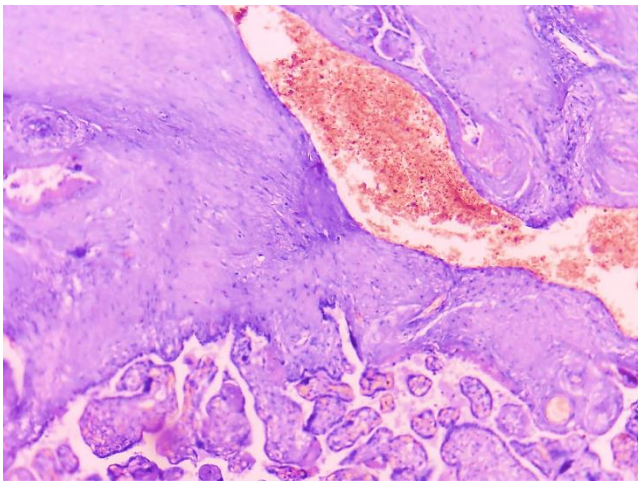


Figure 5. Placental tissue. Thrombosis and hyperplasia of arteriole walls in basal decidual vessels. Diffuse clusters of erythrocytes in the intervillous space. COVID-19-positive pregnancy group.

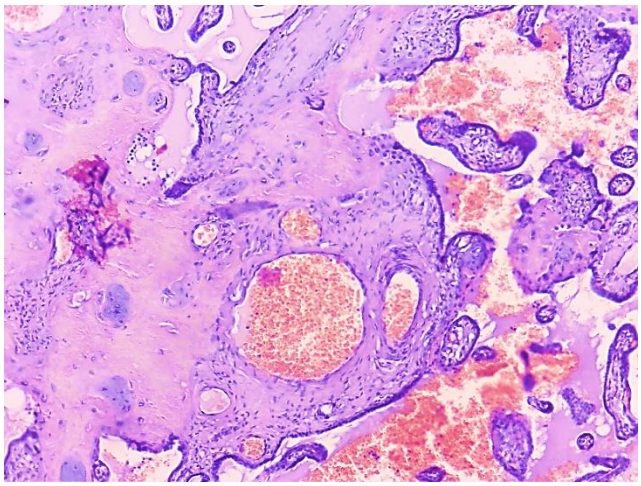


Figure 6. Placental tissue. Fibrinoid edema, acute atherosis, vascular ectasia with clusters of erythrocytes in the intervillous space. COVID-19-positive pregnancy group.

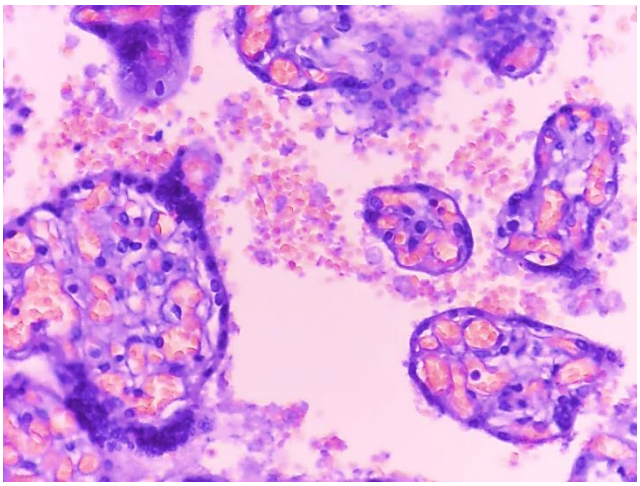


Figure 7. Placental tissue. Arteriolar wall hyperplasia, thrombosis of basal decidual vessels, and clusters of erythrocytes in the intervillous space. COVID-19-positive pregnancy group.

The study shows that pregnant women with COVID-19 (Delta and Omicron variants) have a higher risk of placental histopathological changes than the control group. Significant differences were found in retroplacental hematomas, accelerated villous maturation, villous hypoplasia, arteriole hypertrophy, and dilated vessels. Key findings include a higher rate of chorioangiosis (41.7% vs. 11.9%, P=0.002), fetal chorionic plate thrombosis (18.8% vs. 2.4%, P=0.014), and intramural fibrin deposition (P=0.005). Vascular ectasia was more common in the COVID-19 group (Delta and Omicron variants) with 39.6% of cases compared to 11.9% in the control group (P=0.004, RR=3.3) (Table 4).

Table 4. Comparison of histopathological changes in placentas. Features of fetal vascular malperfusion

Histopathological changes	COVID-19 (n=48)	Control (n=42)	*P* value	Relative Risk (95% CI)
Chorioangiosis	20 (41.7%)	5 (11.9%)	0.002	3.5 (1.4-8.5)
Fetal chorionic plate thrombosis	9 (18.8%)	1 (2.4)	0.014	7.9 (1.5-59.2)
Avascular villi	7 (14.6%)	4 (9.5%)	0.465	1.5 (0.48–4.9)
Villous stromal-vascular karyorrhexis	5 (10.4%)	0	0.032	–
Intramural fibrin deposition	11 (22.9%)	1 (2.4%)	0.005	9.6 (1.3-71.4)
Vascular ectasia	19 (39.6%)	5 (11.9%)	0.004	3.3 (1.4–8.1)

Findings indicated that SARS-CoV-2 infection, particularly the Delta variant, is associated with significant histopathological changes in the placenta, which may have clinical implications for maternal and fetal health.

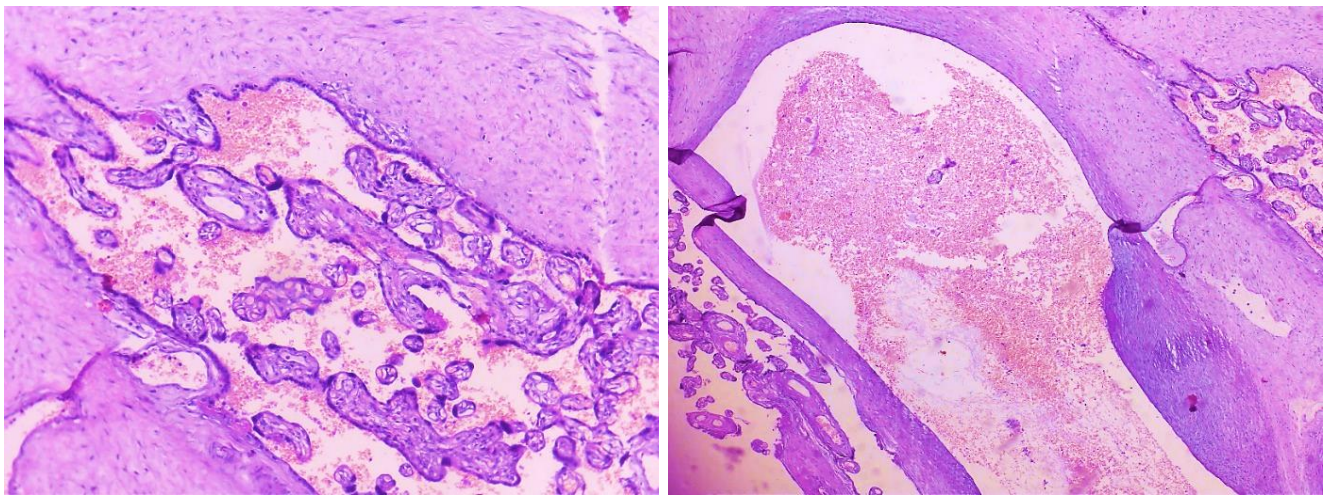
Additional placental changes include (Table 5):

- Intravilous fibrin deposition: 14.6% in Delta cases vs. 2.4% in controls (P=0.043).
- Perivillous fibrin deposits: 70.8% in Delta vs. 21.4% in control (P<0.001).

Table 5. Analysis of additional histopathological changes in the uterus and placenta

Histopathological changes	COVID-19 (n=48)	Control (n=42)	*P* value	Relative Risk (95% CI)
Intravillous fibrin deposition	7 (14,6%)	1 (2,4%)	0,043	6,1 (0,7-7,8)
Perivillous fibrin deposition	34 (70,8%)	9 (21,4%)	<0.001	3,3 (1,8-6,1)
Infarction of the maternal surface of the placenta	7 (14,6%)	3 (7,1%)	0,263	2,0 (0,6-7,4)
Choriomnionitis	13 (27,1%)	5 (11,9%)	0,073	2,3 (0,9-5,9)
Villous agglutination	4 (8,3%)	0 (0,0%)	0,056	-

These findings emphasized the importance of studying the effects of SARS-CoV-2 variants on placental histopathology to better understand infection-related pathologies.

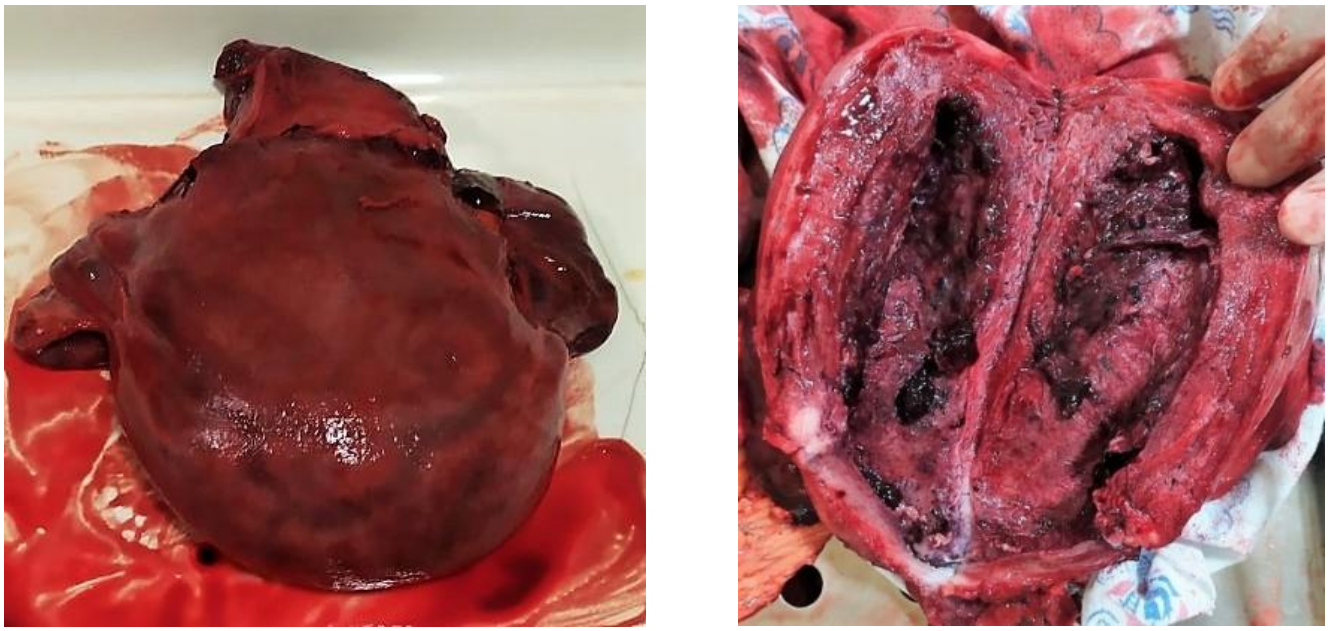


A. B.

Figure 8. A and B. Histopathological examination of placental sections with fetal vascular malperfusion (FVM) against the background of COVID-19: distal villous hyperplasia; fibrinoid necrosis; mural hypertrophy of membranous arterioles; perivillous fibrin deposition; vascular ectasia; chorioangiosis.

Findings of macroscopic uterine in the COVID-19 group

The uterus appeared intact, dark reddish-brown, with a smooth surface, swollen veins, areas of edema, and prominent stasis (Figure 9).



A. B.

Figure 9. Macroscopic view of the uterus in postpartum women with COVID-19. A: uterus with intact structure, smooth surface, dark reddish-brown color, with markedly swollen, edematous veins showing areas of congestion and B: Uterus with generally low consistency, dark reddish-brown color, and areas of hemorrhage.

Histopathological (microscopic) examination of the uterus revealed (Figures 10-12):

- Focal necrosis with dilation of endometrial arteriole lumens;
- Generalized myometrial edema and significant hyperemia of medium and small-caliber vessels;
- Interstitial edema leading to dissociation of muscle fibers and matrix with minimal lymphocytic infiltration and areas of hemorrhage;
- Swollen clusters of smooth muscle cells with pale eosinophilic cytoplasm and pyknotic necrotic nuclei.

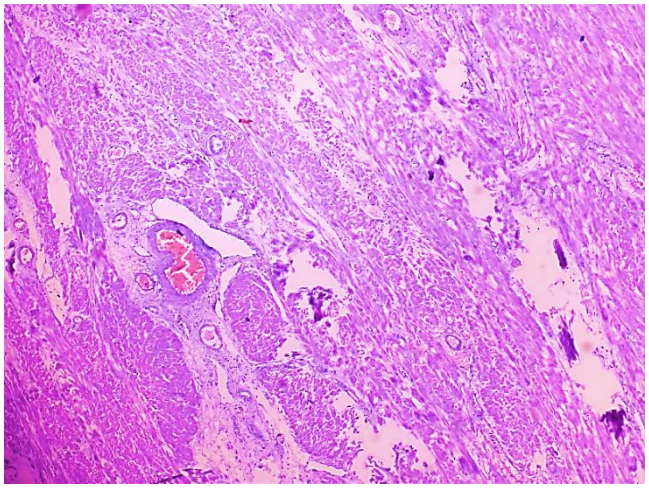


Figure 10. Uterus tissue. Border between the myometrium and decidual tissue. Stromal necrosis, generalized edema of the myometrium, and significant hyperemia of medium and small caliber vessels. Group of pregnant women infected with COVID-19 (Omicron variant).

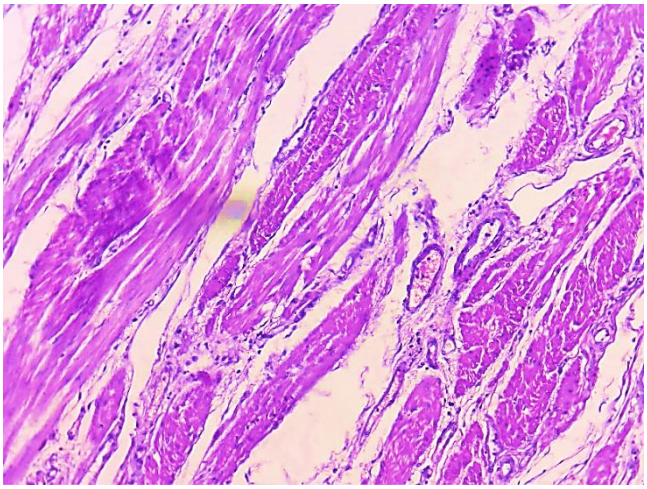


Figure 11. Uterus tissue. Interstitial edema led to the dissociation of muscle fibers and muscle matrix with minimal lymphocytic cell infiltrates and areas of hemorrhage. Group of pregnant women infected with COVID-19 (Delta variant).

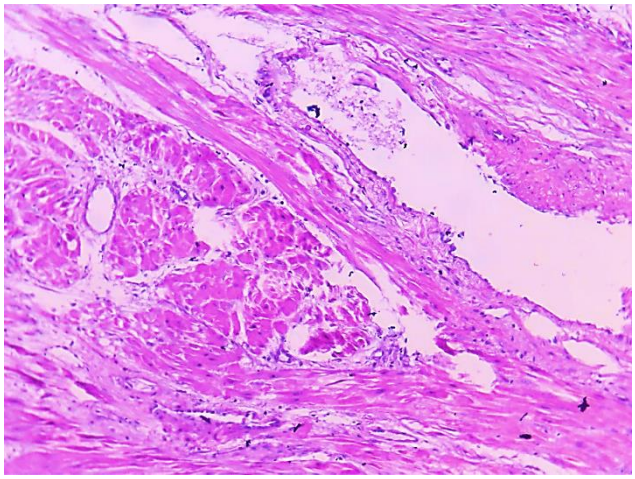


Figure 12. Uterus tissue. Swollen clusters of smooth muscle cells with pale eosinophilic cytoplasm and pyknotic necrotic nuclei. Myometrium with diffuse edema, predominantly localized in perivascular areas. Group of pregnant women infected with COVID-19 (Delta variant).

Our study confirmed that placental damage is prevalent in pregnant women who test positive for SARS-CoV-2. In previous studies during the initial COVID-19 pandemic wave, signs of placental damage and newborn outcomes were comparable between pregnant women with COVID-19 and control groups, suggesting that this could be characteristic of a mild course of COVID-19 and uteroplacental insufficiency in pregnant women with COVID-19.

DISCUSSION

This study investigated histopathological changes in the placenta and uterus of pregnant women testing positive for SARS-CoV-2. We conducted a prospective analytical study that included histological results from 48 symptomatic pregnant women with SARS-CoV-2 (Delta and Omicron variants) and singleton pregnancies. A control group of 42 SARS-CoV-2-negative women with uteroplacental insufficiency, matched by maternal and gestational age, was used. We performed histopathological analyses of the postpartum placenta and uterus, following the "Amsterdam Consensus Criteria for Placental Vascular Malperfusion."

The results of this study will help deepen the understanding of the impact of coronavirus infection on the structure and function of the placenta and uterus, which is critical for developing effective management strategies for pregnancy in women infected with SARS-CoV-2. Baseline characteristics were similar across study groups. The results showed that markers of maternal placental vascular malperfusion were significantly more pronounced in COVID-19-positive pregnancies, including retroplacental hematomas, accelerated villous maturation, distal villous hyperplasia, atherosis, fibrinoid necrosis, hypertrophy of membranous arterioles, vascular ectasia, and persistence of intramural endovascular trophoblast. Fetal placental surface malperfusion in COVID-19-positive cases included chorioangiosis, chorionic plate thrombosis, intramural fibrin deposition, and vascular ectasia, with perivillous fibrin deposits also more common in the COVID-19 group.

Microscopic examination of the uterus in COVID-19-positive pregnancies revealed focal necrosis with arteriole dilation, generalized myometrial edema, significant vessel hyperemia, interstitial edema leading to dissociation of muscle fibers, minimal lymphocytic infiltration, and clusters of swollen smooth muscle cells.

Several distinctions in uteroplacental insufficiency (UPI) manifestations were observed between Delta and Omicron SARS-CoV-2 variants. The Delta variant is generally associated with more severe forms of COVID-19 than the Omicron variant, resulting in more pronounced clinical manifestations of UPI and more significant pathological changes in the placenta and uterus (Table 3, Figures 3-7, Figures 10-12).

Studies showed that the Delta variant causes more pronounced vascular changes, such as arteriole dilation, fibrinoid necrosis, and villous hyperplasia [13-15]. In contrast, the Omicron variant, with its modified genetic structure, may present less aggressively, causing milder placental and uterine pathology [16, 17]. The more severe Delta variant may increase the risk of serious complications in pregnant women, affecting perinatal outcomes [18]. The milder Omicron variant typically does not cause such pronounced pathology, potentially reducing risks for the mother and fetus [13].

These differences highlight the importance of distinguishing the effects of different SARS-CoV-2 strains on UPI and their clinical implications for pregnant women. With increasing disease severity, UPI amid COVID-19

pneumonia may affect pregnancy outcomes, suggesting that disease duration might also influence significant placental dysfunction, given that most infections occur late in the third trimester.

Comparative analysis of histological markers in UPI cases with COVID-19 pneumonia indicated predominant maternal placental malperfusion markers, such as retroplacental hematomas, villous hyperplasia, distal villous hyperplasia, acute atherosis/fibrinoid necrosis, arteriolar hypertrophy, vascular ectasia, and persistent intramural endovascular trophoblast.

Among fetal vascular malperfusion markers in COVID-19 pneumonia with UPI, chorioangiosis, intramural fibrin deposits, vascular ectasia, and perivillous fibrin deposits were most common. Additional markers included villous infarcts, persistent endovascular trophoblast, stable arteriolar hypertrophy, basal decidual vessel thrombosis, avascular villi, chorionic plate thrombosis, villous stromal karyorrhexis, and other signs of intravillous fibrin deposition, maternal surface infarcts, chorioamnionitis, and villous agglutination, though these were not statistically significant compared to controls.

Analyzing these pathomorphological indicators in COVID-19 groups (Table 3) showed a milder course with the Omicron variant than the Delta variant, suggesting a less complicated pregnancy course. In our study, histopathological signs of maternal and fetal surface vascular malperfusion in the placenta were significantly more pronounced in COVID-19 cases than in the control group.

Aurioles-Garibay et al. [13] reported that the presence of villous infarcts and retroplacental hematomas indicated placental hypoperfusion and are common findings in preeclamptic pregnancies. Placental infarcts may result from microthrombi, fibrin deposits, and occlusion of placental spiral arteries. We found significantly higher rates of retroplacental hematomas and villous infarcts.

Turowski et al. [19] stated that perfusion disturbances can lead to changes such as accelerated villous maturation and subsequent distal villous hyperplasia due to poor development of the distal villous tree. Another histopathological feature of vascular malperfusion is decidual arteriopathy, including acute atherosis, fibrinoid necrosis, basal vessel thrombosis, arteriolar hypertrophy, and persistent intramural endovascular trophoblast. Acute atherosis/necrosis is caused by abnormal remodeling of spiral arteries following persistent hypoxic placental injury

In our histological examinations, placental samples from COVID-19 UPI cases showed higher levels of atherosis and arteriolar hypertrophy (Table 3, Figure 6), suggesting that placental decidual arteriopathy is associated with COVID-19 infection.

CONCLUSION

This study identified distinct histopathological changes in the placenta and uterus of pregnant women with COVID-19, with more severe alterations associated with the Delta variant than the Omicron variant. The Delta variant was linked to pronounced vascular malperfusion and greater risks of uteroplacental insufficiency, potentially impacting perinatal outcomes more severely than the less aggressive Omicron variant. These findings underscore the importance of variant-specific considerations in managing pregnancy in COVID-19-positive patients.

DECLARATIONS

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Authors contributions

All authors contributed equally to this work.

Ethical approval

The review board and ethics committee of Republican Specialized Hospital Zangiota-1 approved the study protocol and informed consents were taken from all the participants. All methods were performed in accordance with the relevant guidelines and the principles of Helsinki Declaration.

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Competing interests
All authors declare that they have no conflict of interest.

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