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COVID-19 tanılı gebelerde hastalığın şiddetine göre plasental patolojilerin karşılaştırılması

Comparison of placental pathologies in pregnant women with COVID-19 according to disease severity

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ÖZ

Amaç: COVID-19 tanılı gebelerde hastalığın şiddetine göre plasental patolojileri değerlendirmeyi amaçladık.

Gereçler ve yöntem: Bu retrospektif çalışma Nisan 2020 ile Şubat 2023 tarihleri arasında üçüncü basamak bir merkezde gerçekleştirildi. SARS-CoV-2 pozitif olan 3. trimesterdaki 125 gebenin plasentası incelendi. Plasental patolojiler modifiye edilmiş Amsterdam kriterlerine göre sınıflandırıldı. 104 hasta şiddetli olmayan COVID-19 hastalarından, 21 hasta ise şiddetli COVID-19 hastalarından oluşturularak 2 gruba ayrıldı. Hastalığın şiddetine göre plasental patoloji sonuçları karşılaştırıldı.

Bulgular: MVM (maternal vasküler malpergüzyon) ve FVM (fetal vasküler malperfüzyon) patolojileri şiddetli olmayan grupta 90.4% ve 45.2% olarak izlendi. Şiddetli COVID-19 grubunda ise 71.4% ve 19% ile anlamlı olarak daha düşük izlendi (sırasıyla p=0.018 ve p=0.026). Şiddetli grupta gecikmiş villöz olgunlaşma (GVO) oranı 9.5% olarak izlenirken, şiddetli olmayan grupta 1% olarak izlendi ve bu istatistiksel olarak anlamlıydı (p=0.019). İnflamatuar patolojiler ve diğer patolojik bulgular her iki grupta benzer izlendi. Yoğun bakım ünitesine kabul (YBÜ), eşlik eden maternal hastalık, doğum sonrası komplikasyon şiddetli grupta istatistiksel anlamlı olarak daha yüksek izlendi (p<0.05).

Sonuç: MVM ve FVM lezyonları şiddetli olmayan SARS-CoV-2 hastalarında daha yüksek oranda izlenirken GVO lezyonları ve normal plasentalar şiddetli grupta daha fazla izlendi. SARS-CoV-2 hastalarında hastalığın şiddetine göre farklı plasenta patolojilerinin bulunması, hastalığın akut veya kronik seyri ile ilişkilendirilebilir.

Anahtar Kelimeler: plasental patoloji, SARS-CoV-2, retroplasental hematom

ABSTRACT

Aims: To evaluate the placental pathologies of pregnant women diagnosed with COVID-19 according to disease severity.

Materials and method: This retrospective study was conducted at a tertiary center between April 2020 and February 2023. The placentas of 125 pregnant women in their third trimester who were positive for SARS-CoV-2 were examined. Placental pathologies were classified according to the modified Amsterdam criteria. According to the disease severity, the patients were divided into two groups: non-severe COVID-19 (n=104) and severe COVID-19 (n=21). Placental pathology results were compared between the two groups.

Results: The rates of maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM) were 90.4% and 45.2% in the non-severe COVID-19 group. Whereas it was significantly lower at 71.4% and 19% in the severe COVID-19 group (p=0.018 and p=0.026, respectively). The rate of delayed villous maturation (DVM) was 9.5% in the severe COVID-19 group and 1% in the non-severe COVID-19 group, indicating a statistically significant difference (p=0.019). Inflammatory pathologies and other pathological findings were similar between the two groups. Intensive care unit (ICU) admission, presence of accompanying maternal diseases, and postpartum complications were statistically significantly higher in the severe COVID-19 group (p<0.05).

Conclusion: Whereas MVM and FVM lesions were observed at a higher rate in patients with non-severe COVID-19, DVM lesions and normal placentas were more common in those with severe COVID-19. The presence of different placental pathologies in SARS-CoV-2 patients according to the severity of the disease may be associated with the acute or chronic course of the disease.

Keywords: placental pathology, SARS-CoV-2, retroplacental hematoma

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic by the World Health Organization (WHO) in March 2010 (1). SARS-CoV-2 is a novel coronavirus that can cause serious global health problems in pregnant women (2). SARS-CoV-2 infection during pregnancy is associated with numerous adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth, particularly in those with the clinically severe form of the disease (3).

Severe COVID-19, in particular, causes persistent hypoxia that results in the development of preeclampsia, fetal growth restriction (FGR), and stillbirth in pregnant women. As the maternal-fetal interface, the placenta not only plays an important role in protecting the fetus from infections but can also be affected by maternal diseases (4). Therefore, the placenta is like a diary of pregnancy, with its histopathological examination providing valuable information concerning the health of both the mother and the fetus (5). Although COVID-19 is primarily an infection of the respiratory tract, viremia is detected in up to 40% of COVID-19 cases, leading to extrapulmonary manifestations that involve multiple organs, including the placenta (6).

Studies have shown that women with the SARS-CoV-2 infection have an increased risk of placental lesions due to hypoperfusion and inflammation (7). The potential association between SARS-CoV-2 and impaired placental function is very important, since it can lead to fetal decompensation and an increased risk of perinatal mortality and morbidity (8). Although there are many studies examining the placenta of SARS-CoV-2-positive patients, there is no known placental finding specific to the disease (9).

In this study, we aimed to evaluate placental pathologies and perinatal outcomes in patients with COVID-19 according to disease severity.

MATERIAL AND METHODS

Ethics Committee Approval

This retrospective cohort study was conducted at a tertiary center between April 2020 and February 2023. The study was approved by Medical Research Ethics Unit and carried out in accordance with the tenets of the Declaration of Helsinki (E2-23-3584).

Study design and population

The primary endpoint of the study was placental pathologies in SARS-CoV-2-positive patients according to disease severity. The second endpoint was the relationship between placental pathology results and perinatal outcomes.

Due to the SARS-CoV-2 testing protocol being universally applied during the study period, the real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was performed in all pregnant women at the time of their hospitalization (10). The diagnosis of COVID-19 was made based on a positive RT-PCR test result from combined oropharyngeal and nasopharyngeal swab samples. Severe COVID-19 was defined as the presence of dyspnea, a respiratory rate of 30 or more per minute, an oxygen saturation of 93% or less in room air, or findings consistent with pneumonia. Non-severe COVID-19 was accepted as a positive RT-PCR result for SARS-CoV-2 without severe signs and symptoms (11).

The study group consisted of 125 participants selected from SARS-CoV-2-positive pregnant women according to the RT-PCR test. According to disease severity, the patients were divided into two groups: non-severe (n = 104) and severe (n = 21) COVID-19. The demographic data, clinical features, obstetric histories, pregnancy outcomes, and placental pathologies of the patients were obtained from the hospital information system and patient files and recorded in a case report form.

The placentas of SARS-CoV-2-positive patients were sent for pathology evaluation at the discretion of the obstetricians. Placental histopathological findings observed more than once in patients were categorized separately. PCR samples were not taken from the placentas for the diagnosis of COVID-19. Multiple pregnancies, patients with known fetal anomalies, and those whose placentas were not histopathologically examined were excluded from the study.

Histopathological examination and data collection

The Amsterdam Placental Workshop Group Consensus Statement on Sampling and Definitions of Placental Lesions was used to define placental pathologies. Accordingly, the histopathological results were grouped into six categories, and umbilical cord abnormalities were also evaluated as the seventh category (12, 13):

1. Maternal vascular malperfusion (MVM), including placental infarction, syncytial knots, perivillous and intervillous fibrin deposition, subchorionic, retroplacental and intervillous hemorrhage, and placental necrosis.

2. Fetal vascular malperfusion (FVM), including submembra-

nous hemorrhage, chorangiosis, calcifications, and degenerative changes.

3. Delayed villous maturation (DVM).

4. Inflammatory pathologies, including acute and chronic subchorionitis, chorioamnionitis, acute villitis, intervillositis, and deciduitis.

5. Other pathological findings, such as subamniotic cysts, meconium, and villous edema.

6. A normal placenta with no pathological finding

7. Umbilical cord abnormalities, including hydropic degeneration and a single umbilical artery

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) was used to enter and analyze the data. The Kolmogorov-Smirnov test was conducted to determine whether the data conformed to a normal distribution. The Mann-Whitney U test was used for the variables that did not show a normal distribution (non-parametric) between the two groups. The chi-square test was undertaken for the comparison of categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

The sample consisted of a total of 125 SARS-CoV-2-positive pregnant women who gave birth in our hospital and underwent a placental examination over the study period. Of these women, 104 had non-severe COVID-19 and 21 had severe COVID-19. Table 1 presents the demographic characteristics, clinical characteristics, and perinatal outcomes of all participants. Age, body mass index, gravida, parity, intrauterine fetal death, and placental weight were similar between the severe and non-severe COVID-19 groups. Maternal oxygen saturation, week of birth, fetal birth weight, and first- and fifth-minute APGAR scores were statistically significantly lower in the severe COVID-19 group ($p < 0.05$). The length of hospital stays, intensive care unit admission, presence of accompanying maternal diseases, and postpartum complications were statistically significantly higher in the severe COVID-19 group ($p < 0.05$). The rate of cesarean section was also significantly higher in the severe COVID-19 group than in the non-severe COVID-19 group (85.7% and 52.9%, respectively, $p = 0.005$). Concerning labor indications, the initiation of labor due to maternal reasons was observed at a rate of 47.6% in the severe COVID-19 group and 2.9% in the non-severe COVID-19 group ($p < 0.001$).

Table 1. Comparison of the study groups in terms of demographic characteristics, clinical features, and perinatal outcomes.

	Non-severe COVID-19 (n = 104)	Severe COVID-19 (n = 21)	P value
Maternal age (years)	30 (8.5)	35 (10.5)	0.473
BMI (kg/m²)	29.4 (4.2)	28.6 (4.75)	0.237
Gravida	2 (1.5)	2 (1)	0.777
Parity	1 (2)	1 (2)	0.169
COVID-19 diagnosis (day)*	5 (5.5)	5 (6)	0.309
Oxygen saturation**	97 (1)	89 (3.5)	**<0.001**
Week of birth	37 (4.5)	35 (6)	**<0.001**
Delivery type, n (%)			
Cesarean section	55 (52.9%)	18 (85.7%)	**0.005**
Vaginal delivery	49 (47.1%)	3 (14.3%)	
Delivery indications, n (%)			
Maternal	3 (2.9%)	10 (47.6%)	**<0.001**
Obstetric	101 (97.1%)	11 (52.4%)	
Length of hospital stay (day)	2 (2)	8 (11.5)	**<0.001**
ICU admission, n (%)	1 (1%)	10 (47.6%)	**<0.001**
Maternal disease, n (%)	22 (21.2%)	7 (33.3%)	**<0.001**
Postpartum complications, n (%)	3 (2.9%)	10 (47.6%)	**<0.001**
Fetal birth weight (g)	2900 (1085)	2270 (1470)	**0.004**
First-minute APGAR score	8 (1)	7 (4)	**0.005**
Fifth-minute APGAR score	9 (0.5)	9 (3.5)	**0.003**
NICU admission, n (%)	18 (17.3)	13 (61.9)	**<0.001**
Intrauterine fetal death, n (%)	8 (7.7)	2 (9.5)	0.778
Placental weight (g)	540 (165.5)	540 (238)	0.453

Data presented as median (interquartile range) or count (percentage). $P < 0.05$ accepted as statistically significant.

(BMI: body mass index, kg: kilogram, m²: square meters, ICU: intensive care unit, g: gram, NICU: neonatal intensive care unit)

*Time elapsed since COVID-19 diagnosis.

**Maternal oxygen saturation at the time of presentation to the hospital.

The placental pathology results of the severe and non-severe COVID-19 groups are given in Table 2.

Table 2. Comparison of the study groups in terms of placental pathologies.

	Non-severe COVID-19 (n = 104)	Severe COVID-19 (n = 21)	P value
Maternal vascular malperfusion, n (%)	94 (90.4%)	15 (71.4%)	**0.018**
Placental infarction	31 (29.8%)	5 (23.8%)	0.580
Syncytial knots	28 (26.9%)	4 (19%)	0.451
Perivillous fibrin deposition	78 (75%)	13 (61.9%)	0.219
Subchorionic hemorrhage	4 (3.8%)	1 (4.8%)	0.845
Intervillous fibrin deposition	6 (5.8%)	1 (4.8%)	0.855
Retroplacental hemorrhage	0 (0)	1 (4.8%)	**0.025**
Placental necrosis	12 (11.5%)	1 (4.8%)	0.353
Intervillous hemorrhage	69 (66.3%)	13 (61.9%)	0.696
Fetal vascular malperfusion, n (%)	47 (45.2%)	4 (19%)	**0.026**
Submembranous hemorrhage	9 (8.7%)	0 (0)	0.162
Chorangiosis	8 (7.7%)	0 (0)	0.189
Calcification	33 (31.7%)	4 (19%)	0.245
Degenerative changes	4 (3.8%)	0 (0)	0.361
Delayed villous maturation, n (%)	1 (1%)	2 (9.5%)	**0.019**
Inflammatory pathologies, n (%)	18 (17.3%)	5 (19%)	0,849
Acute subchorionitis	9 (8.7%)	4 (19%)	0.155
Chorioamnionitis	3 (2.9%)	0 (0)	0.431
Acute villitis	2 (1.9%)	0 (0)	0.522
Chronic subchorionitis	3 (2.9%)	0 (0)	0.431
Intervillositis	3 (2.9%)	0 (0)	0.431
Deciduitis	1 (1%)	1 (4.8)	0.206
No pathology (normal), n (%)	1 (1%)	3 (14.3%)	**0.002**
Other placental findings, n (%)	9 (8.7%)	1 (4.8%)	0.549
Subamniotic cyst	1 (1%)	0 (0)	0.652
Meconium	2 (1.9%)	0 (0)	0.522
Villous edema	6 (5.8%)	1 (4.8%)	0.855
Umbilical cord abnormalities, n (%)	4 (3.8%)	3 (14.3%)	0.058
Hydropic degeneration	3 (2.9%)	2 (9.5%)	0.157
Single umbilical artery	1 (1%)	1 (4.8%)	0.206

Data presented as count (percentage). P < 0.05 accepted as statistically significant.

Placental histopathological findings observed more than once in patients were categorized separately.

The rates of MVM and FVM were statistically significantly higher in the non-severe COVID-19 group (p = 0.018 and p = 0.026, respectively). In the severe COVID-19 group, the rate of DVM was 9.5%, which was statistically significantly higher than that of the non-severe COVID-19 group (1%) (p = 0.019). The rate of patients with normal placental pathology results was 14.3% in the severe COVID-19 group and 1% in the non-severe COVID-19 group (p = 0.002). Inflammatory pathologies and other pathological findings were similar between the two groups. When the subcategories of placental histopathological findings were examined, while retroplacental hematoma was more common in the severe COVID-19 group (p=0.025), the other placental histopathological findings were similar between the two groups. Additionally, umbilical cord abnormalities were observed at a higher rate in the severe COVID-19 group, but the difference was not statistically significant (p = 0.058).

CONCLUSION

This study evaluated placental pathologies of patients diagnosed with COVID-19 according to disease severity. The results showed that the MVM and FVM pathologies were more common in the non-severe COVID-19 group, whereas villous maturation loss and normal placentas were more common in the severe COVID-19 group. It was determined that inflammatory pathologies and other pathological findings did not significantly differ according to the severity of COVID-19. When the subcategories of placental pathology findings were examined, the patients with severe COVID-19 had a significantly higher rate of retroplacental hemorrhage, while the remaining findings were similar between the two groups.

Placental pathologies can sometimes indicate a process requiring immediate treatment or provide information to explain findings in the antepartum and peripartum periods. Another important role of these pathologies is to reveal underlying processes that may explain long-term adverse outcomes for the fetus and mother (14). Placental pathologies can result from abnormalities in one of the three vascular compartments of pregnancy, namely the maternal circulation, the fetal circulation, and the placental parenchyma itself (15). Microorganisms can infect the placenta through either the transvaginal or hematogenous route due to disrupted placental integrity or an impaired immune

system (16). Nevertheless, the findings of some studies did not reveal any evidence of vertical transmission of SARS-CoV-2 in early pregnancy (17). Placental pathologies in maternal COVID-19 disease can be attributed to the systemic, localized, or direct effect of SARS-COV-2 on the placenta (18).

In the literature, it has been debated whether maternal SARS-CoV-2 infection affects pregnancy outcomes or placental histopathologies (19). A systemic review and meta-analysis of 42 studies found that COVID-19 disease was associated with poor perinatal outcomes, such as preterm birth, low fetal birth weight, and neonatal intensive care unit admission (20). The mechanisms involved in poor pregnancy outcomes in women infected with SARS-CoV-2 were considered to be virus-induced chronic inflammation, chronic virus presence in the uterine bed, or abnormal angiogenesis of the local uterine/placental microenvironment (21). Although the initial examinations of the placentas of SARS-CoV-2-positive women showed evidence of vascular lesions and thrombosis, there are conflicting reports concerning whether such lesions occur on the fetal or maternal side of the placenta (22). A study investigating placental pathologies associated with COVID-19 reported that the placental histopathology results of women who were PCR-positive for SARS-CoV-2 in their third trimester did not significantly differ from those of PCR-negative controls at a similar gestational age (23). We also wanted to evaluate placental pathologies in COVID-19 patients according to the severity of the disease.

In a systemic review and meta-analysis of 56 studies reporting placental pathologies in pregnant women with the SARS-CoV-2 infection, the histopathological result was MVM in 30.7% of the patients, FVM in 27.1%, acute inflammation in 22.7%, and chronic inflammation in 25.7%. Similar results were found in the subgroup analyses performed based on the presence of maternal symptoms or high-risk pregnancy (24). In another meta-analysis comparing 699 SARS-CoV-2-positive pregnant women and 18,326 SARS-CoV-2-negative controls, no significant difference was observed between the groups in terms of MVM, FVM, and inflammatory pathologies (25). We observed a higher rate of MVM pathologies in COVID-19 patients in this study.

MVM reflects structural changes caused by an impaired maternal blood supply to the feto-placental unit (21). MVM pathologies are associated with important clinical sequelae, such as preterm birth, fetal growth retardation, and fetal death. Maternal hypoxia secondary to a severe COVID-19 lung infection may initiate inadequate uterine perfusion, followed by hypoxic-ischemic damage to the placenta (12). A previous study reported that the placentas of 14 (93%) of 15 SARS-CoV-2-positive patients in their third trimester had at least one MVM finding, most commonly infarction and increased fibrin deposition, compared to healthy controls that had a much lower rate of MVM at 30% (26). Similarly, in the current study, MVM lesions were the most common findings, observed at a rate of 90.4% in the non-severe COVID-19 group and 71.4% in the severe COVID-19 group.

FVM encompasses multiple histological signs of thrombosis, indicating the obstruction of fetal blood flow, usually secondary to cord obstruction or a hypercoagulable state, and its risk factors are similar to those of other coagulopathic processes (27). SARS-CoV-2 tends to cause dysfunction in endothelial cells, leading to a state of complement-induced coagulopathy in patients infected with COVID-19, making them susceptible to microthrombus formation (28). In a previous study, FVM pathologies were detected in the placentas of 40% of SARS-CoV-2-positive patients (29). Similarly, we observed FVM pathologies in 45.2% of the patients in the non-severe COVID-19 group and 19% of those in the severe COVID-19 group. This may be related to a more chronic course of non-severe COVID-19.

Exposure to intrauterine inflammation and placental changes can potentially result in poor perinatal outcomes (30). The placentas of patients infected with SARS-CoV-2 may show the inflammatory, thrombotic, and vascular changes found in other inflammatory conditions (9). In a study examining the placenta of 419 pregnant women with the SARS-CoV-2 infection, inflammation was the most common finding at a rate of 54.8%, and no relationship was found between placental abnormalities and the SARS-CoV-2 infection (31). In addition, conducted with 36 SARS-CoV-2-positive patients, the rate of inflammatory pathologies in the placental examination was 34.7% (12). In our study, inflammatory pathologies were observed at similar rates in the severe and non-severe COVID-19 groups and did not correlate with disease severity. The reason for this may be the development of inflammatory pathologies secondary to factors such as premature rupture of membranes (PROM).

In term placentas with DVM, the increased placental barrier or structural immaturity for gestational age causes fetal morbidity, including fetal hypoxia and spontaneous preterm delivery (32). In a previous study, the frequency of DVM was reported to be significantly higher in cases of fetal death compared to controls (33). Rebutini et al. examined the placentas of 19 SARS-CoV-2 positive patients, six (31.5%) had DVM (34). In our study, the rate of DVM was found to be significantly higher in patients with severe COVID-19. This pathological finding may be valuable,

considering the higher rate of poor perinatal outcomes in the severe COVID-19 group.

Glynn et al. examined the timing of delivery and the presence of infections, it was shown that placental pathologies varied according to the timing of delivery. The authors found that the placentas of patients who gave birth during the acute SARS-CoV-2 infection were more likely to have FVM lesions, while those of patients with a history of SARS-CoV-2 infection remote from delivery were more likely to have MVM lesions (19). In another study examining the placentas of SARS-CoV-2-positive patients in their third trimester, no significant difference was observed between the placental pathologies of the symptomatic and asymptomatic groups (23). Our results differing according to disease severity may be related to the acute or chronic course of COVID-19.

A striking finding of our study was the higher incidence of MVM and FVM lesions in patients with non-severe COVID-19. Possible reasons for this include the more acute course of COVID-19 and the earlier initiation of labor, mostly due to maternal causes, in severe cases, while patients with non-severe COVID-19 can have an asymptomatic or mildly symptomatic disease course for a long time, have indications for labor with the deterioration of fetal well-being due to obstetric reasons, are incidentally diagnosed with COVID-19 at the time of the spontaneous onset of labor, and have a more chronic disease course.

Limitations

This study has certain limitations. First, it was conducted in a single center with a small sample size. Second, it had a retrospective design. Third, it was not known when the patients who were asymptomatic at the time of hospitalization contracted SARS-CoV-2. Lastly, the PCR test for SARS-CoV-2 was not performed on placental samples, which can be the subject of future studies. There is also a need for multicenter studies with larger samples.

CONCLUSIONS

Our study showed that MVM and FVM lesions were more commonly detected in the placentas of patients with non-severe COVID-19. We found a higher rate of DVM and normal placentas in the severe COVID-19 group. Inflammatory pathologies and other pathological findings did not seem to be affected by disease severity. Adverse pregnancy outcomes were observed at a higher rate in patients with severe COVID-19. Further studies are needed to investigate the relationship between placental pathologies and the severity of COVID-19.

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