Original Article

HISTOPATHOLOGICAL CHANGES IN THE PLACENTAS OF MOTHERS WITH A HISTORY OF CORONAVIRUS DISEASE 2019 INFECTION IN PREGNANCY: A COMPARATIVE CROSS-SECTIONAL STUDY

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ABSTRACT

This study aimed to evaluate histopathological changes in the placentas of mothers who had contracted COVID-19 during pregnancy. This prospective study involved the histopathological assessment of two groups of placentas submitted for evaluation to the Department of Histopathology at Khoula Hospital, Oman. The first group consisted of 48 placentas derived from COVID-19-positive pregnant women delivered at the centre between March 2020 and March 2021. The control group consisted of an additional 48 placentas derived from asymptomatic mothers who were not tested for COVID-19 but were assumed to be negative. All placentas underwent gross and microscopic histopathologic examination. Placental lesions were classified according to the Amsterdam system. There was a significantly higher frequency of fibrin thrombi at the terminal villi in placentas derived from the COVID-19-positive group compared to the control group (72.9% versus 0%; *p-value* = 0.001). Also, villous hypoperfusion was significantly more common in COVID-19-positive placentas than in controls (16.7% versus 0%; *p-value* = 0.006). However, no significant differences between the two groups were noted with regards to the frequency of other histopathologic features, including decidual vasculopathy, chorioamnionitis, funisitis, intervillositis, perivillous fibrin deposition, and infarction.

Key Words: Placenta, COVID-19, SARS-CoV-2, maternal infection, histopathology.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by a new strain of coronavirus belonging to the severe acute respiratory syndrome (SARS) family, known as SARS-CoV-2. The virus was previously unreported in humans and genetically similar to the strain responsible for causing the SARS outbreak in 2003 (1). Patients infected with COVID-19 may present with a wide range of symptoms from fever, fatigue, and cough to severe complications such as shortness of breath and chest pain or even acute respiratory distress syndrome, septic shock, multiorgan failure, coagulopathy, and death (2). Transmission occurs by inhaling contaminated droplets and close contact with infected persons and contaminated surfaces (3).

The initial outbreak of COVID-19 was first reported in Wuhan, China, in December 2019, and has since spread rapidly over the last two years into a global pandemic with millions of confirmed cases and deaths worldwide (1, 2). However, inconsistent findings have been reported in the literature with regards to the possibility of transplacental transmission and placental changes as a result of

COVID-19 infection during pregnancy. Several studies and case reports have suggested the possibility of transplacental transmission, of which some have reported fetal deaths attributed to COVID-19 (4-11). On the other hand, other researchers have suggested that transmission of the infection is not possible during pregnancy due to the placental fetomaternal barrier (12-15).
Moreover, conflicting data and differing histological findings have been noted in placentas derived from cases of positive COVID-19 infections (16-18). Some studies have demonstrated that COVID-19 infection is associated with significant placental hypoperfusion, decidual vasculopathy, and other features of maternal vascular malperfusion (19-23). Another study also described elements of fibrin deposition, chronic intervillositis, and trophoblast necrosis (24). In general, there is limited information available regarding the effect of SARS-CoV-2 infection on the placenta overall, and no previous research has yet been conducted to assess this topic in Oman. Therefore, the objective of the this study was to evaluate histopathological changes in the placentas of women in Oman who had contracted COVID-19 during pregnancy.

METHODS

This prospective comparative cross-sectional study was conducted at the Department of Histopathology of Khoula Hospital, a tertiary reference hospital that receives cases from all *wilayats* (counties) of Muscat Governorate, Oman. All placentas submitted for histopathological evaluation to the department were included in this study. Placentas in the case group were derived from COVID-19-positive pregnant women who had delivered at the hospital between March 2020 and March 2021, during the peak of the pandemic in Oman. Eligible cases included placentas derived from pregnant women with laboratory-confirmed diagnoses of COVID-19 infection with polymerase chain reaction (PCR) testing for SARS-CoV-2 using nasopharyngeal swabs collected during their antenatal check-ups or at the time of delivery. Only the placentas of those who had delivered at 26–40 gestational weeks were sent for gross and microscopic histopathological examination. Placentas derived from women who had delivered at ≤25 gestational weeks were excluded from the analysis. For comparison, an equal number of placentas were derived from asymptomatic women with no significant close contact with COVID-19-positive cases and had not undergone PCR testing for COVID-19 during pregnancy or at the time of delivery were included. As per the hospital's institutional policy, patients were tested for COVID-19 only if they were symptomatic or reported having had close contact with positive cases. However, as placentas from healthy patients are not routinely sent for histopathological examination, placentas in the control group included those submitted for evaluation due to specific indications such as poor fetal outcome or concerning obstetric history, including intrauterine growth restriction (IUGR), oligohydramnios, chronic hypertension, pregnancy-induced hypertension (i.e., gestational hypertension as well as pre- or postpartum pre-eclampsia), pre-existing or gestational diabetes, and coagulopathy.
Placentas for both cases and controls underwent gross and microscopic histopathological examination. Placental lesions were identified according to the Amsterdam classification system (25). The placentas were fixed in 10% buffered formalin for 72 hours or longer. The gross examination included recording the placental weight, placental disc dimensions, and a description of the umbilical cord, membranes, and any lesions. Sections submitted for analysis included 3-mm-thick tissue sectioned at 5-mm intervals of various parts of the placenta, including the membrane rolls, two cross-sections from the umbilical cord, two full-thickness sections of the placental disc, and representative sections of any lesions. All sections underwent routine processing and were embedded in paraffin

blocks; subsequently, the cut tissue (4-µm) was placed on glass slides and stained using hematoxylin and eosin (H&E) before being submitted for microscopic examination. Two experienced pathologists reviewed histologic findings using the Amsterdam classification system (25).

STATISTICAL METHODS

The COVID-19 infection status of the cases and controls was determined from information gathered using the electronic medical record system and information regarding obstetric and fetal outcomes. Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 23.0 (IBM Corp., Armonk, New York). Descriptive statistics were used to describe the characteristics of the sample. Frequencies and percentages were reported for categorical variables, whereas means and standard deviations were used to present continuous variables. Pearson's Chi-squared (χ^2) test or Fisher's exact test (for low cell frequencies) was used to assess significance as appropriate, with a p-value of ≤0.05 considered statistically significant.

RESULTS

A total of 96 placentas submitted for evaluation to the histopathology department were included in the study, out of which 48 were cases (i.e. COVID-19-positive), and there was an equal number controls (i.e. COVID-19-negative) (n = 48 each). The mean gestational age of the infected and control groups was 37.5 ± 2.5 weeks (range: 26-40 weeks) and 35.25 ± 5.2 weeks (range: 15-41 weeks), respectively. In the case group, the timing of COVID-19 testing varied, with 16 cases (33%) testing positive on the day of delivery, 16 (33%) within the week prior to delivery, 12 (25%) two weeks before delivery, and four (8%) more than two weeks before delivery.

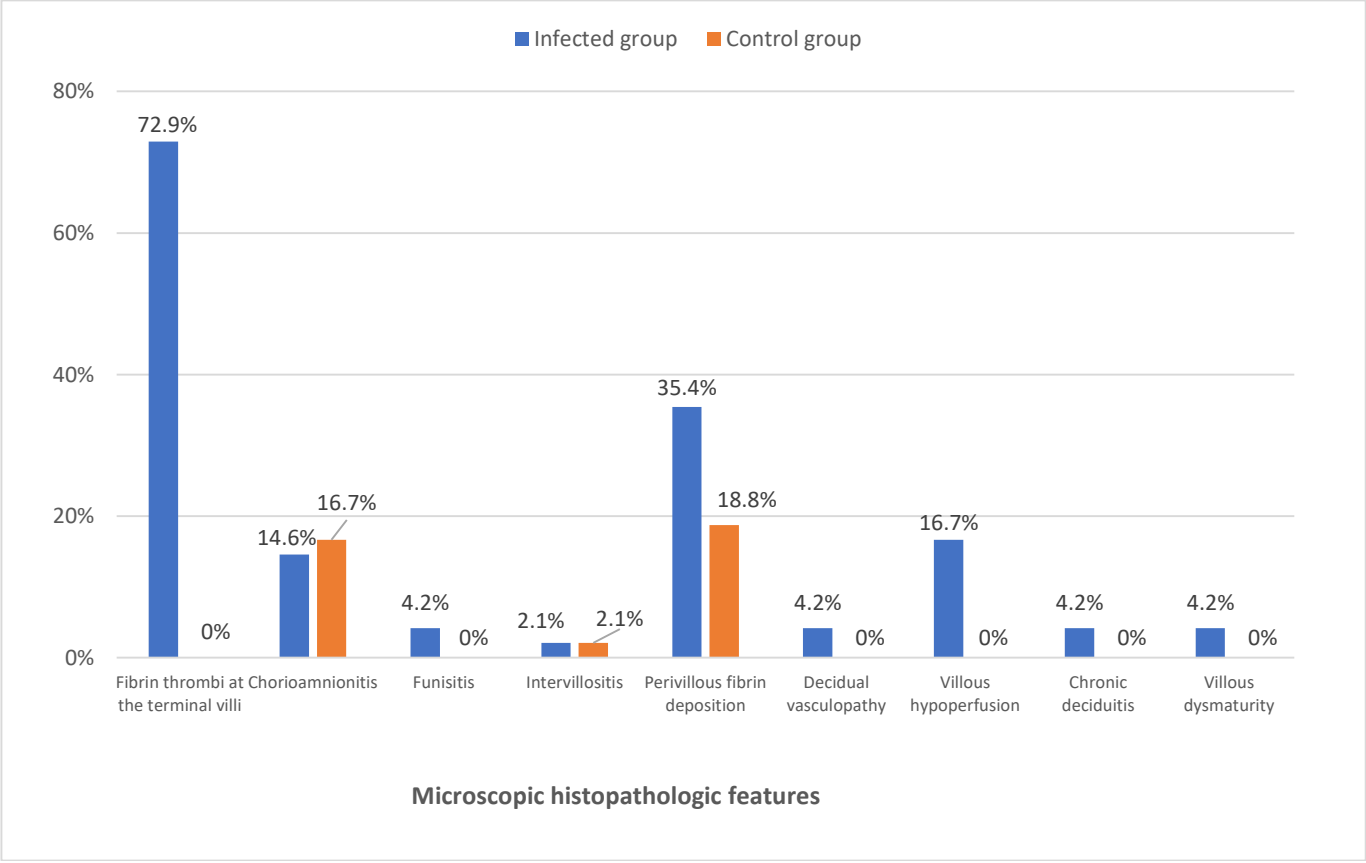

Figure. 1. Bar chart comparing the frequency of microscopic histopathological findings between control placentas and those derived from mothers with a history of COVID-19 infection in pregnancy

The H&E-stained slides of placentas in both the control and case groups were examined. Figure 1 illustrates the frequency of microscopic findings recorded in both groups, including fibrin thrombi at the terminal villi, perivillous fibrin deposition, decidual vasculopathy, chorioamnionitis, villous hypoperfusion, funisitis, and intervillositis. Two statistically significant differences between the groups were observed. First, there was a significantly higher frequency of fibrin thrombi at the terminal villi in placentas derived from COVID-19-positive cases compared to controls (72.9% versus 0%; p-value = 0.001) (Figure 2a). Second, villous hypoperfusion was significantly more common in COVID-19-positive placentas compared to controls (16.7% versus 0%; p-value = 0.006) (Figure 2b).

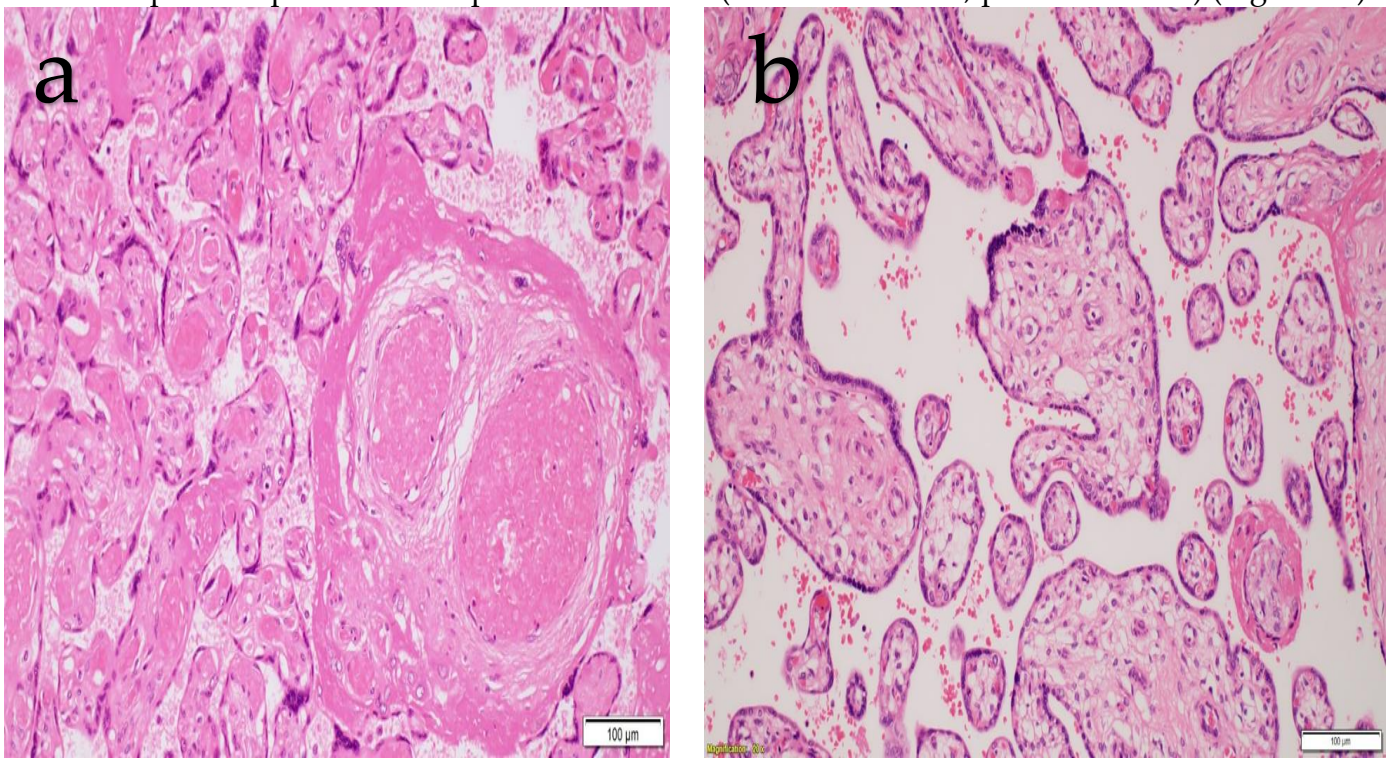

Figure. 2. (a) H&E-stained slide of placental tissue derived from a COVID-19-positive pregnant woman showing fibrin thrombi at the terminal villi. (b) H&E-stained slide of placental tissue derived from a COVID-19-positive pregnant woman showing villous hypoperfusion

In contrast, no significant differences were noted between cases and controls with regards to the frequency of other histopathological features, including decidual vasculopathy, chorioamnionitis, funisitis, intervillositis, perivillous fibrin deposition, and infarction (Figure 3a-d). With regards to neonatal outcomes, there was a higher frequency of intrauterine fetal death (IUFD) (31.3% versus 10.4%; p-value = 0.023) and prematurity (22.9% versus 6.3%; p-value = 0.023) in the control group compared to the case group (Table 1). However, no significant association was found between COVID-19 infection status and low-birth-weight (<2.5 kg) infants (6.3% versus 4.2%; p-value = 0.87).

Table 1. Comparison of Pregnancy Outcomes in Mothers with and without a History of COVID-19 Infection in Pregnancy (N = 96).

		Outcome, n (%)				Total
		Healthy	Intrauterine Fetal Death	Anomaly	Premature birth	
Group	Infected	40 (83.3)	5 (10.4)	0 (0)	3 (6.3)	48
	Control	20 (41.6)	15 (31.3)	2 (4.2)	11 (22.9)	48

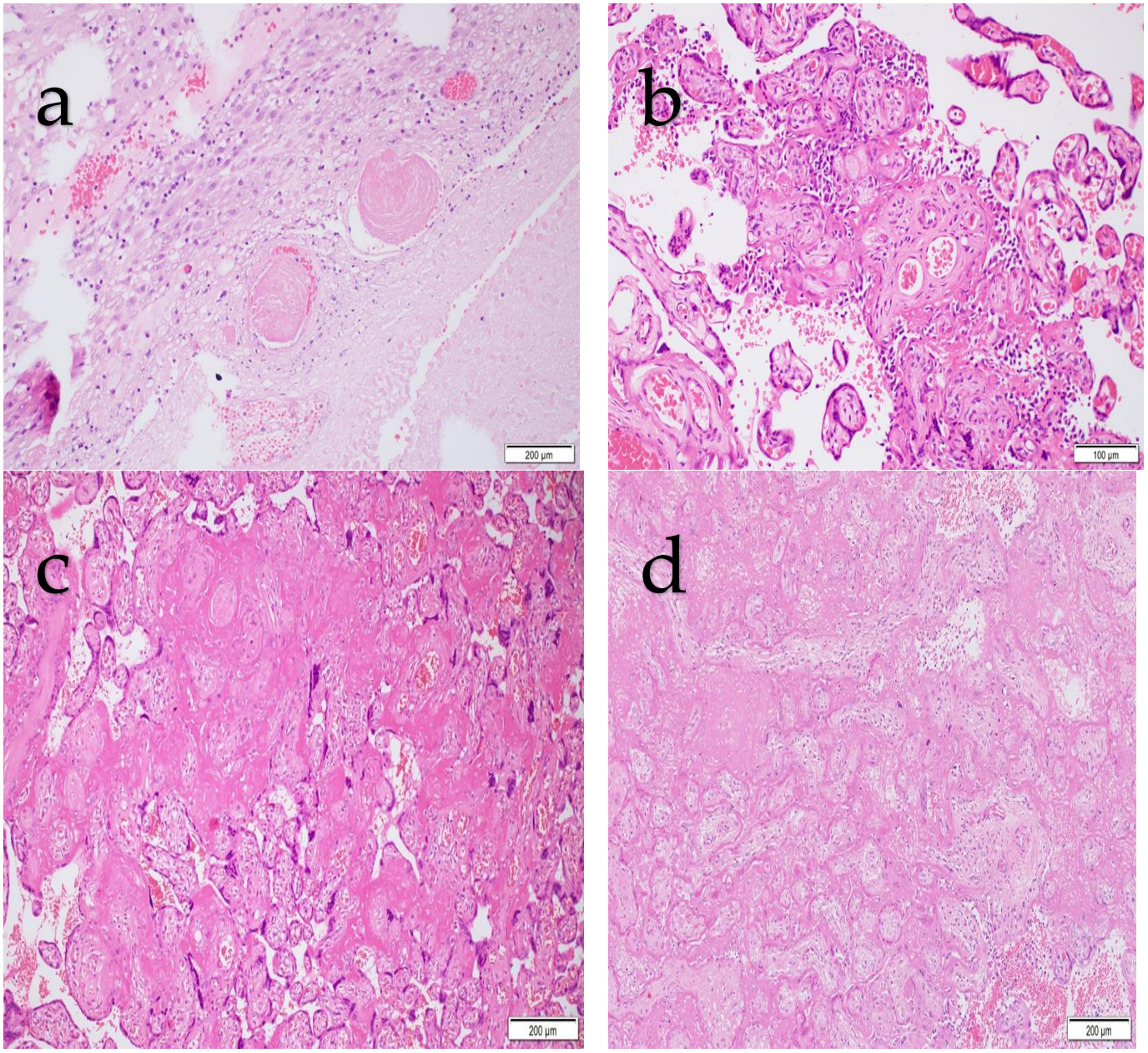

Figure. 3. Hematoxyline and Eosin slides of placental tissue derived from COVID-19-positive pregnanct woman (a) Showing thrombi within decidual blood vessels in a case of maternal vasculopathy. (b) Showing chronic intervillositis. (c) Showing intervillous fibrin deposition. (d) Showing infarction of villi

DISCUSSION

To date, limited information is known regarding the effect of COVID-19 on the human placenta and whether vertical transmission of the infection from mother to infant is possible. Several studies have sought to assess the pathology of the placenta in COVID-19-positive mothers, with varying results (16-24). In the current study, a statistically significant relationship was observed between COVID-19 infection status and the presence of fibrin thrombi within the terminal villi blood vessels (72.9% versus 0%; *p-value* = 0.001). This finding may represent underlying pregnancy-specific sequelae of COVID-19-associated coagulopathy. Similar findings have been reported by Menter *et al*. (21).

Our study further demonstrated a significant relationship between COVID-19 infection status and the frequency of villous hypoperfusion (16.7% versus 0%; *p-value* = 0.006). Villous hypoperfusion is primarily caused by the narrowing and reduction of the number of terminal villi blood vessels; specifically, 25% of cases of villous hypoperfusion in the present study demonstrated terminal vil-

lous thrombi. Fetal vascular narrowing is usually diagnosed via the morphometric analysis of placental material in the clinical context of marked IUGR and abnormal pulsed flow Doppler results. However, in our study, information regarding history of IUGR was not available and Doppler studies were not performed. Nevertheless, several previous studies have shown significant findings of fetal vascular malperfusion. Glynn *et al*. found that fetal vascular malperfusion lesions were significantly more frequent among pregnant patients with a history of acute SARS-CoV-2 infection (26). Similarly, Baergen and Heller demonstrated that 50% of COVID-19-positive mothers in their study showed some evidence of fetal vascular malperfusion, including intramural vascular thrombosis, villous stromal-vascular karyorrhexis, and intramural non-occlusive thrombi (27).

No statistically significant differences in the frequency of other microscopic findings were observed in the present study, including perivillous fibrin deposition, maternal vasculopathy, chorioamnionitis, funisitis, intervillositis, and villous dysmaturity. Similar histological findings were also observed in other studies without statistical significance (9, 11, 28, 29). In particular, perivillous fibrin deposition was apparent in 17 (35.4%) of the placentas derived from COVID-19-infected patients; however, this feature was also present in 11 (22.9%) placentas in the control group. Singh *et al*. reported that the main placental histopathologic findings in a series of COVID-19-infected patients were increased fibrin in addition to microcalcifications, syncytial knotting, and villous agglutination (30). Other case reports have found the main histological findings to be intervillositis (24, 31, 32) and infarction (22). Such features were not observed in the present study. In addition, several researchers have indicated that the frequency of maternal vascular malperfusion is significantly higher in placentas derived from SARS-CoV-2-positive pregnancies (13, 20-23, 33). However, this finding was not statistically significant in our study, with only two COVID-19-positive cases (4.2%) showing maternal vasculopathy.

Moreover, there was no statistical difference in terms of gestational age between cases and controls in our study, with 40 (83.3%) patients in the COVID-19 positive group having full-term normal deliveries and only three (6.3%) going into premature labor at 26–36 gestational weeks. This finding was also noted in other studies (6, 25). On the other hand, the control group showed a high proportion of premature births (n = 11; 22.9%). Moreover, there was a significantly increased frequency of IUFD among control cases (31.3% versus 10.4%; $p = 0.023$). This was likely because only the placentas of mothers with a concerning obstetric history are usually submitted for histopathological evaluation.

Of the five cases of IUFD in COVID-19-positive mothers, three (60%) were born premature and one was full term. The causes of both the prematurity and IUFD varied, including maternal hypertension, polyhydramnios, and severe symptomatic maternal COVID-19 infection. In the existing literature, cases of fetal death have been reported in women with confirmed COVID-19 infection, severe clinical symptoms, and premature delivery (12), as well as those with confirmed COVID-19 infection without any significant clinical or obstetric disorders, thereby suggesting that fetal demise may be a possible outcome of COVID-19 infection in pregnancy (6, 34). Two studies involving 106 and 50 cases of SARS-CoV-2 infection in pregnancy, respectively, did not show any IUFD (23, 26). In addition, no statistically significant relationship between COVID-19 infection and low birth weight was found in the current study (6.3% versus 4.2%; $p = 0.87$). Similar observations have been made in other studies (22, 27).

While the findings of our study can be considered reliable, generalizability is limited due to the sampling procedure, given that the samples were collected from a single center. In addition, it is important to note that the placentas in the control group were derived from mothers with poor or concerning obstetric histories since healthy placentas are not routinely sent for histopathological

examination. Moreover, women in the control group were not tested for COVID-19 infection and were presumed to be COVID-19-negative because they were asymptomatic or had had no close contact with COVID-19-positive cases, as per hospital protocol. Finally, since the duration of infection in some cases was short or the infection was only diagnosed on the day of delivery, some infected cases might not yet have shown any histological changes at the time of analysis.

CONCLUSION

In summary, placentas derived from COVID-19-positive mothers showed a significantly increased prevalence of terminal villous thrombi and fetal vascular malperfusion relative to the controls. The findings of this research are important as COVID-19 is still an emerging disease, and such results may help clinicians and obstetricians in their future decision-making.

ETHICAL CONSIDERATION

Ethical approval for this study was obtained from the Research Ethics Committee of the Directorate General of Khoula Hospital, Ministry of Health, Oman (PRO022021077). This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. This study involved no direct contact with patients, as all placentas were submitted directly to the histopathology department for evaluation. Consent to evaluate the placentas utilized in this study was granted by the Research Ethics Committee of the Directorate General of Khoula Hospital, Ministry of Health, Oman.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

None to declare.

AUTHORS' CONTRIBUTIONS

H.K conceived the presented research idea and went through literature review. N.M and S.A under the supervision of H.K. designed the research methodology and have reviewed the slides. N.M and S.A. were involved in the data collection and date entry. N.M, S.A, M.G and H.K analyzed and interpreted the results. H.K. was a major contributor in writing the manuscript in consultation with M.G. and R.K. H.K was the research supervisor who guided N.M and S.A throughout the project. All authors read and approved the final manuscript.

REFERENCES

1. World Health Organization: WHO coronavirus (COVID-19) dashboard. 2021. https://covid19.who.int. Accessed May 18, 2021.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. Liu Y, Ning Z, Chen Y, Guo M, Liu Y, Gali NK, Sun L, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature. 2020;582(7813):557-560.
4. Richtmann R, Torloni MR, Oyamada Otani AR, Levi JE, Crema Tobara M, de Almeida Silva C, Dias L, et al. Fetal deaths in pregnancies with SARS-CoV-2 infection in Brazil: a case series. Case Rep Womens Health. 2020;27:e00243.

5. Valdespino-Vázquez MY, Helguera-Repetto CA, León-Juárez M, Villavicencio-Carrisoza O, Flores-Pliego A, Moreno-Verduzco ER, Díaz-Pérez DL, et al. Fetal and placental infection with SARS-CoV-2 in early pregnancy. J Med Virol. 2021;93(7):4480-4487.
6. Sukhikh G, Petrova U, Prikhodko A, Starodubtseva N, Chingin K, Chen H, Bugrova A, et al. Vertical transmission of SARS-CoV-2 in second trimester associated with severe neonatal pathology. Viruses. 2021;13(3):447.
7. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, Mangili G, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020;2(3):100145.
8. Facchetti F, Bugatti M, Drera E, Tripodo C, Sartori E, Cancila V, Papaccio M, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. EBioMedicine. 2020;59:102951.
9. Colson A, Depoix CL, Dessilly G, Baldin P, Danhaive O, Hubinont C, Sonveaux P, et al. Clinical and in vitro evidence against placenta infection at term by severe acute respiratory syndrome coronavirus 2. Am J Pathol. 2021;191(9):1610-1623.
10. Zadorosnei Rebutini P, Zanchettin AC, Schueda Stonoga ET, Marani Prá DM, Parmegiani de Oliveira AL, da Silva Dezidério F, Simoneti Fonseca A, et al. Association between COVID-19 pregnant women symptoms severity and placental morphologic features. Front Immunol. 2021;12:685919.
11. Bouachba A, Allias F, Nadaud B, Massardier J, Mekki Y, Bouscambert Duchamp M, de la Fourniere B, et al. Placental lesions and SARS-Cov-2 infection: diffuse placenta damage associated to poor fetal outcome. Placenta. 2021;112:97-104.
12. Dong L, Pei S, Ren Q, Fu S, Yu L, Chen H, Chen X, et al. Evaluation of vertical transmission of SARS-CoV-2 in utero: nine pregnant women and their newborns. Placenta. 2021;111:91-96.
13. Gao L, Ren J, Xu L, Ke X, Xiong L, Tian X, Fan C, et al. Placental pathology of the third trimester pregnant women from COVID-19. Diagn Pathol. 2021;16(1):8.
14. Giordano G, Petrolini C, Corradini E, Campanini N, Esposito S, Perrone S. COVID-19 in pregnancy: placental pathological patterns and effect on perinatal outcome in five cases. Diagn Pathol. 2021;16(1):88.
15. Jani S, Jacques SM, Qureshi F, Natarajan G, Bajaj S, Velumula P, Agu C, et al. Clinical characteristics of mother-infant dyad and placental pathology in COVID-19 cases in predominantly African American population. AJP Rep. 2021;11(1):e15-e20.
16. Patberg ET, Adams T, Rekawek P, Vahanian SA, Akerman M, Hernandez A, Rapkieqicz AV, et al. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. Am J Obstet Gynecol. 2021;224(4):382.e1-382.e18.
17. Gulersen M, Prasannan L, Tam Tam H, Metz CN, Rochelson B, Meirowitz N, Shan W, et al. Histopathologic evaluation of placentas after diagnosis of maternal severe acute respiratory syndrome coronavirus 2 infection. Am J Obstet Gynecol MFM. 2020;2(4):100211.
18. Tasca C, Rossi RS, Corti S, Anelli GM, Savasi V, Brunetti F, Cardellicchio M, et al. Placental pathology in COVID-19 affected pregnant women: a prospective case-control study. Placenta. 2021;110:9-15.
19. Di Girolamo R, Khalil A, Alameddine S, D'Angelo E, Galliani C, Matarrelli B, Buca D, et al. Placental histopathology after SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2021;3(6):100468.

20. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in COVID-19. Am J Clin Pathol. 2020;154(1):23-32.
21. Menter T, Mertz KD, Jiang S, Chen H, Monod C, Tzankov A, Waldvogel S, et al. Placental pathology findings during and after SARS-CoV-2 infection: features of villitis and malperfusion. Pathobiology. 2021;88(1):69-77.
22. Resta L, Vimercati A, Cazzato G, Mazzia G, Cicinelli E, Colagrande A, Fanelli M, et al. SARS-CoV-2 and placenta: new insights and perspectives. Viruses. 2021;13(5):723.
23. Moresi S, Dell'Aquila M, Salvi S, Rullo R, Fruci S, Stollagli F, Arena V, et al. SARS-CoV-2 infection in pregnancy: clinical signs, placental pathology, and neonatal outcome - implications for clinical care. Front Med (Lausanne). 2021;8:676870.
24. Watkins JC, Torous VF, Roberts DJ. Defining severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) placentitis: a report of 7 cases with confirmatory in situ hybridization, distinct histomorphologic features, and evidence of complement deposition. Arch Pathol Lab Med. 2021;145(11):1341-1349.
25. Khong TY, Mooney EE, Ariel I, Balmus NCM, Boyd TK, Brundler MA, Derricott H, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016;140(7):698-713.
26. Glynn SM, Yang YJ, Thomas C, Friedlander RL, Cagino KA, Matthews KC, Riley LE, et al. SARS-CoV-2 and placental pathology: malperfusion patterns are dependent on timing of infection during pregnancy. Am J Surg Pathol. 2022;46(1):51-57.
27. Baergen RN, Heller DS. Placental pathology in COVID-19 positive mothers: preliminary findings. Pediatr Dev Pathol. 2020;23(3):177-180.
28. Hecht JL, Quade B, Deshpande V, Mino-Kenudson M, Ting DT, Desai N, Dygulska B, et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. Mod Pathol. 2020;33(11):2092-2103.
29. Husen MF, van der Meeren LE, Verdijk RM, Fraaij PLA, van der Eijk AA, Koopmans MPG, Freeman L, et al. Unique severe COVID-19 placental signature independent of severity of clinical maternal symptoms. Viruses. 2021;13(8):1670.
30. Singh N, Buckley T, Shertz W. Placental pathology in COVID-19: case series in a community hospital setting. Cureus. 2021;13(1):e12522.
31. Hosier H, Farhadian SF, Morotti RA, Deshmukh U, Lu-Culligan A, Campbell KH, Yasumoto Y, et al. SARS-CoV-2 infection of the placenta. J Clin Invest. 2020;130(9):4947-4953.
32. Linehan L, O'Donoghue K, Dineen S, White J, Higgins JR, Fitzgerald B. SARS-CoV-2 placentitis: an uncommon complication of maternal COVID-19. Placenta. 2021;104:261-266.
33. Jaiswal N, Puri M, Agarwal K, Singh S, Yadav R, Tiwary N, Tayal P, et al. COVID-19 as an independent risk factor for subclinical placental dysfunction. Eur J Obstet Gynecol Reprod Biol. 2021;259:7-11.
34. Poisson TM, Pierone G Jr. Placental pathology and fetal demise at 35 weeks of gestation in a woman with SARS-CoV-2 infection: a case report. Case Rep Womens Health. 2021;30:e00289.