Original Article

Placental Pathology in SARS-CoV-2 Infection During Second and Third Trimester: A Study in a Tertiary Care Center

Sucheta Devi Khuraijam*, Pratima Devi Khumanthem, Sushma Khuraijam, Sheronica Laishram, Robedi Choudhurimayum, Opendro Singh Narengbam

Regional Institute of Medical Sciences, Imphal, Manipur, India

DOI: 10.21276/APALM.3401

***Corresponding Author**:
Dr Sucheta Devi Khuraijam
sucheta.kh73@gmail.com

Submitted: 09-Jul-2024
Final Revision: 17-Sep-2024
Acceptance: 28-Sep-2024
Publication: 06-Oct-2024

Abstract

Background: The pandemic caused by the novel coronavirus named SARS-CoV-2 (COVID-19) has affected millions. As of June 2024, the number of deaths has reached more than 7.1 million across the globe. The clinical spectrum ranges from mild respiratory tract infection to life-threatening complications and death. Pregnant women are a particular group, and pathological changes in the placentas of SARS-CoV-2 positive patients are needed to understand the effects and outcomes of pregnancy. This study was conducted to assess any specific placental histopathology related to COVID-19.

Materials and Methods: We conducted a cross-sectional study on all placentas from women who were COVID-19 positive during the second and third trimesters of pregnancy in the Department of Pathology of a tertiary care center in Northeast India.

Results: We encountered twelve (12) placentas from COVID-19 positive mothers. There were nine (75%) live births and three (25%) intrauterine fetal deaths. Features of maternal vascular malperfusion, such as increased perivillous and intervillous fibrin, were the most common findings. Chorangiosis and avascular villi were the most common features of fetal vascular malperfusion. Also observed were marked macrophage infiltration (CD 68 positive), chorioamnionitis, and calcification.

Conclusion: Infection with COVID-19 has adverse clinical outcomes and significant placental histopathological and immunohistochemistry findings.

Keywords:

Placenta, pathology, COVID-19, immunohistochemistry, fetal death

Introduction

The pandemic caused by the novel coronavirus SARS-CoV-2 (COVID-19) has affected millions. As of June 2024, the number of deaths has reached more than 6.8 million across the globe [1]. The clinical spectrum ranges from mild respiratory tract infection to life-threatening complications like respiratory failure, heart failure, septic shock, coagulopathy, etc. [2].

Pregnant women are a particular group, and because of the characteristic immune response, they are at risk of severe morbidity and even mortality. Severe adverse pregnancy outcomes are associated with coronaviruses causing Severe Acute Respiratory Syndrome (SARS), Middle-East Respiratory Syndrome (MERS), and SARS-CoV-2 (COVID-19) [3, 4, 5, 6]. Many studies report unfavorable pregnancy outcomes such as maternal hypertension, preeclampsia, HELLP syndrome, intrauterine growth retardation

(IUGR), premature birth, intrauterine death (IUD), stillbirth, etc., which are associated with certain placental pathologies like maternal vascular malperfusion (MVM) [7, 8, 9]. The exact pathophysiological mechanisms are not fully recognized. However, errors in the remodeling of the uterine vasculature appear to be a critical step leading to malperfusion. Absence of remodeling of spiral arterioles and sequential luminal occlusions result in hypoxic-ischemic injury, causing infarction of the placental parenchyma [8]. The abnormality of placental development can be detected by serial sonography as abnormal uterine artery Doppler waveforms, low levels of pregnancy-associated placental protein A (PAPP-A), and placental growth factors (PlGF) [9].

Low serum maternal PlGF levels (<100 pg/mL) are associated with early-onset preeclampsia, IUGR, premature birth, and stillbirth. Features of MVM are found in the placentas of these cases following delivery [8]. Hence, the level of maternal PlGF can be used to identify patients with chronic placental ischemia, which will help in timely intervention. Further studies on pathological changes and inflammatory responses using immunohistochemistry (IHC) in the placentas of COVID-19 positive patients are needed to understand the effects and outcomes of pregnancy. If MVM features are detected in these placentas, serial ultrasound observations of placental formation and uterine artery Doppler, along with serial maternal circulating angiogenic growth factor levels, may be recommended in pregnancies with COVID-19 infection to reduce adverse outcomes.

In this study, we aim to assess any specific placental histopathological findings in mothers who were COVID-19 positive during the second or third trimester and correlate these with pregnancy outcomes. We also plan to evaluate the pattern of reaction in the placenta using immunohistochemical markers CD3, CD20, CD68, CD138, CD10, and CD34.

Materials and Methods

Clinical Data Collection: This is a cross-sectional study conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology of a tertiary care center in North-East India. We included all consecutive cases of placentas from COVID-19 positive mothers received in the histopathology section during the six-month study period from July 2021 to December 2021. We obtained ethical clearance from the institutional Research Ethics Board. The study included placentas from pregnant women positive in the second and third trimesters of pregnancy (13-42 weeks). We excluded placentas from pregnant women who were negative for SARS-CoV-2 infection during pregnancy, had complications like severe pregnancy-induced hypertension, and infections such as TORCH. We collected all the required clinical data.

Histopathological Examination: Placentas were brought to the Department of Pathology from the Department of Obstetrics and Gynaecology under strict COVID-19 protocol. We fixed the placentas in 10% buffered formalin and grossed the specimen 48 hours later. We took one block from the umbilical cord, three from the placenta, and one from the membranes. We also sampled from areas of significant gross changes like infarction, hemorrhage, and calcification. All the tissue sections were stained with Haematoxylin and Eosin to look for histopathological findings. We recorded the pathological findings using the Amsterdam Placental Workshop Group Consensus statement [10]. Two pathologists examined all the slides to validate the findings.

Immunohistochemical Studies: We selected six primary antibodies, namely anti-B cell (CD20), anti-T cell (CD3), anti-Hofbauer cell (CD10), anti-macrophage (CD68), anti-plasma cell (CD138), and anti-endothelial cell (CD34). The first five antibodies helped in identifying the infiltrating cells, and CD34 helped in the identification of blood vessels and their pathology. The antibodies for IHC are from Master Diagnostica, Spain.

Statistical Analysis: We entered the data into Microsoft Excel and analyzed it using SPSS 26.0 for relevant statistical comparisons. We presented the results in the form of tables and images. Descriptive statistics were performed by calculating means and standard

deviations for the continuous variables, and frequencies and percentages for the categorical variables.

Results

Clinical profile of the 12 cases: We had twelve placentas during the study period. The maternal age ranged from 19 to 35 years, and the gestational age at the time of delivery varied from 23 to 40 weeks, with a mean of 35.5 weeks. The neonatal outcomes in this study included nine live births, two with Intrauterine Growth Retardation (IUGR), and three Intrauterine Fetal Deaths (IUFD).

Pathological details in the placenta of the women with SARS-CoV-2 positivity: Features of maternal vascular malperfusion were present in all 12 cases. Characteristic observations included infarction (3/12), increased perivillous fibrin deposition (9/12) [Fig. 1A], increased intervillous fibrin (9/12) [Fig. 1B], retroplacental hemorrhage (5/12), accelerated villous maturation, decidual vasculopathy, and intervillous thrombosis (1/12 each) [Table 1].

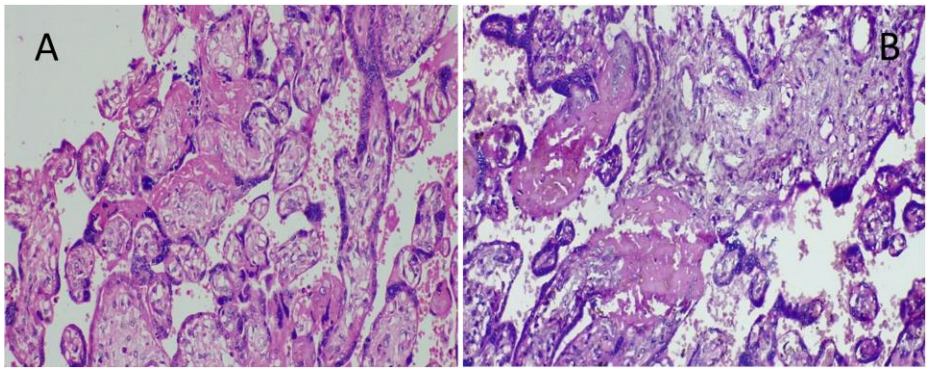

Figure 1: H&E stained (200x) sections showing increased perivillous fibrin deposition (A) and increased intervillous fibrin deposition (B).

We also observed fetal vascular malperfusion in all 12 cases. Features included thrombi in the fetal circulation (2/12), avascular villi (7/12), karyorrhexis (2/12), delayed villous maturation (2/12), and chorangiosis (8/12) [Fig. 2A, Table 1].

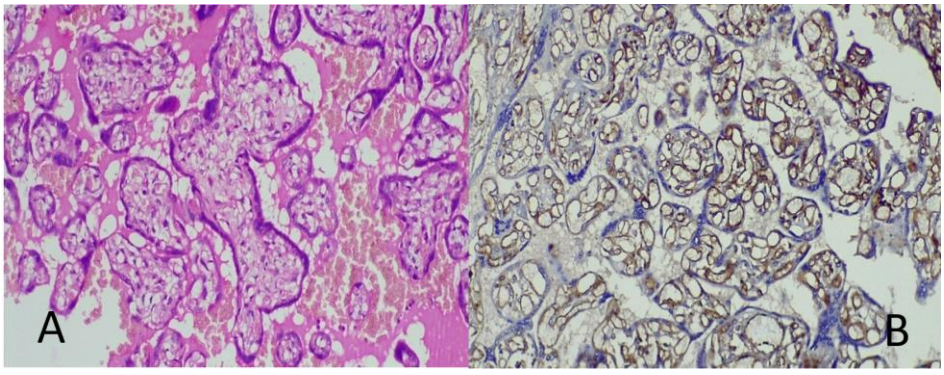

Figure 2: H&E stained (200x) sections showing villi with chorangiosis (A) and CD34immunohistochemistry highlighting the endothelial linings (B).

Inflammatory changes like chorioamnionitis were observed in 7 of the 12 cases, with the predominant cells being macrophages [Table 1, Fig. 3A]. All three IUFD cases displayed standard maternal vascular malperfusion features such as infarction, increased perivillous fibrin, chorangiosis, and chorioamnionitis [Table 2]. The IUGR cases also manifested similar histopathological

features, including increased perivillous and intervillous fibrin deposition, chorangiosis, and chorioamnionitis.

Table 1: Histopathological findings in the placenta (n=12)

Category	Characteristics	Present	Absent
Category 1: Maternal Vascular Malperfusion (MVM)			
i.	Infarction	3	9
ii.	Increased perivillous fibrin deposition	9	3
iii.	Accelerated villous maturation	1	11
iv.	Decidual vasculopathy	1	11
v.	Increased intervillous fibrin	9	3
vi.	Retroplacental haemorrhage	5	7
vii.	Intervillous thrombosis	1	11
Category 2: Fetal Vascular Malperfusion (FVM)			
i.	Thrombi in the fetal circulation	2	10
ii.	Avascular villi	7	5
iii.	Karyorrhexis	2	10
iv.	Delayed villous maturation	2	10
v.	Chorangiosis	8	4
Category 3: Inflammatory Changes			
i.	Chorioamnionitis	7	5
ii.	Chronic villitis	1	11
iii.	Chronic deciduitis	-	-
iv.	Subchorionitis	-	-
v.	Chorio vasculitis	-	-
vi.	Fetal vasculitis	-	-
Category 4: Other Placental Findings			
i.	Accreta	-	-
ii.	Villous edema	-	-
iii.	Hofbauer cell hyperplasia	-	-
iv.	Calcification	8	4

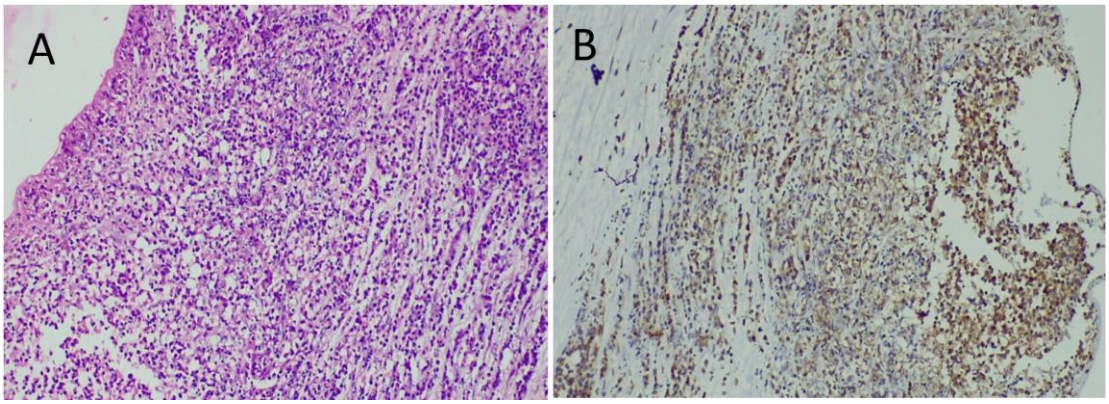

Figure 3: H&E stained (200x) sections showing chorioamnionitis (A) and CD68 immunohistochemistry highlighting the macrophages (B).

Table 2: Histopathological findings in the placenta in IUFD cases(n=3).

Findings	Case 1	Case 2	Case 7
Maternal Age (years)	30	35	20
Gestational Age (weeks)	35	23	33
CS/NVD*	NVD	NVD	NVD
MVM Features			
Infarction	++	+	++
Increased perivillous fibrin deposition	+	+	+
Increased intervillous fibrin	+	+	+
Retroplacental hemorrhage	-	+	+
FVM Features			
Thrombi in the fetal circulation	-	+	-
Avascular villi	-	++	++
Chorangiosis	+	++	++
Inflammatory Changes			
Chorioamnionitis	++	++	+
***IUFD= Intra-uterine fetal death, CS = Caesarean section, NVD = Normal vaginal delivery.**			

Table 3: Histopathological findings in placenta in IUGR* cases (n=2).

Findings	Case 9	Case 12
Maternal Age (years)	36	23
Gestational Age (weeks)	38	37 + 2 days
Comorbid Events	-	-
CS/NVD*	CS	NVD
Birth Weight (kg)	2.1	2.2
MVM Features		
Increased perivillous fibrin deposition	+	+
Increased intervillous fibrin	+	+
FVM Features		
Chorangiosis	+	+
****IUGR = Intra-uterine growth retardation, CS = Caesarean section, NVD = Normal vaginal delivery.**		

Table 4: Comparison of outcomes of pregnancies in COVID-19 positive patients.

Outcomes	Present Study (n=12)	Richtman et al (n=36)	Corn et al (n=4)	Chen et al (n=9)	Liu et al (n=3)	Baergen et al (n=20)	Baral et al (n=20)	Gao et al (n=8)
IUFD	3 (25%)	5 (14%)	3 (75%)	1 (11%)	-	-	1 (11%)	0
IUGR	2 (17%)	-	-	-	-	-	0	0
Favourable	7 (58%)	31 (86%)	1 (25%)	8 (89%)	3 (100%)	20 (100%)	19 (89%)	8 (100%)

Table 5: Histopathological findings in the placentas in different studies.

Category	Characteristics	Present Study (n=12)	Singh N et al (n=50)	Hetch et al (n=19)	Menter T et al (n=5)	Baergen et al (n=20)	Gao et al (n=8)	Zhang P et al (n=74)
Category 1: Maternal Vascular Malperfusion (MVM)								
	Infarction	3 (12%)	13 (26%)	-	2 (40%)	1 (5%)	2 (25%)	9.5%
	Increased perivillous fibrin deposition	9 (75%)	26 (52%)	-	2 (40%)	1 (5%)	8 (100%)	-
	Accelerated villous maturation	1 (8.3%)	20 (40%)	-	0	4 (20%)	1 (12.5%)	-
	Decidual vasculopathy	1 (8.3%)	-	2 (10%)	3 (60%)	1 (5%)	0	33.8%
	Increased intervillous fibrin	9 (75%)	26 (52%)	-	4 (80%)	1 (5%)	-	97.3%
	Retroplacental haemorrhage	5 (42%)	-	-	0	1 (5%)	-	-
	Intervillous thrombosis	1 (8.3%)	-	-	0	1 (5%)	0	-
Category 2: Fetal Vascular Malperfusion (FVM)								
	Thrombi in the fetal circulation	2 (17%)	-	-	2 (40%)	3 (15%)	0	24.3%
	Avascular villi	7 (58%)	14 (28%)	-	0	1 (5%)	0	93.2%
	Karyorrhexis	2 (17%)	-	-	0	3 (15%)	0	-
	Delayed villous maturation	2 (17%)	-	-	1 (20%)	-	-	-
	Chorangiosis	8 (67%)	7 (14%)	-	2 (40%)	-	-	-
Category 3: Inflammatory Changes								
	Chorioamnionitis	7 (58%)	3 (6%)	-	1 (20%)	1 (5%)	0	-
	Chronic villitis	1 (8.3%)	-	-	2 (40%)	4 (20%)	0	23%
	Chronic deciduitis	-	-	-	2 (40%)	-	2 (25%)	-
	Subchorionitis	-	-	-	2 (40%)	-	-	-
	Chorio vasculitis	-	-	-	1 (20%)	-	-	-
	Fetal vasculitis	-	-	-	1 (20%)	-	-	-
Category 4: Other Placental Findings								
	Accreta	-	-	-	-	-	-	-
	Villous edema	-	-	-	-	-	-	-
	Hofbauer cell hyperplasia	-	-	-	-	-	-	-
	Calcification	8 (67%)	30 (60%)	-	-	-	-	-

Placental findings like calcification were observed in 66% (8/12) of the cases, whereas other placental findings, such as placenta accreta, villous edema, and Hofbauer cell hyperplasia, were not observed.

In the immunohistochemical study, we confirmed chorangiosis using CD34 [Fig. 2B]. Marked macrophage infiltration indicated by CD68 positivity [Fig. 3] was seen in 7 out of 12 cases. However, lymphocytic infiltration by B-cells (CD20+) and T-cells (CD3+) was seen in one case each. Hofbauer cells (CD10+) and plasma cells (CD138+) were not increased.

Discussion

Several epidemics and pandemics in the world have been caused by coronaviruses, with the latest being COVID-19 [11]. Prenatal transmission from COVID-19 positive mothers has been documented in some studies [12]. SARS-CoV-2 RNA was present in the placenta, focally in the syncytiotrophoblast and cytotrophoblast, in very few cases in a study done by Hecht JL et al. [13]. However, vertical transmission was confirmed by the demonstration of SARS-CoV-2 spike S1 subunit protein in two of the deceased fetuses born to COVID-19 positive mothers [14].

The placenta is vital for the development of the fetus to its full potential. Any changes in placental function can modify the course of pregnancy and impact the child's health from birth to childhood. During the COVID-19 pandemic, the role of the placenta as a barrier against SARS-CoV-2 infection remains unsolved. Here, we evaluated 12 placentas retrieved from COVID-19 positive mothers and their pregnancy outcomes. The mean maternal age at the time of delivery was 35.5 weeks, which was identical to the studies done by Singh et al. [11], Hecht JL et al. [13], Menter T et al. [15], and Sinaci et al. [16].

Our study had three IUFD and two IUGR cases out of 12, indicating a poor pregnancy outcome, similar to the studies done by Richtman et al. [17] (5 IUD/20 live births) and Corn M et al. [14] (3 IUD/4 live births). However, pregnancies with favorable outcomes were observed in other studies done by Chen et al. [18] (1 IUGR/9 live births), Liu et al. [19] (0 IUGR/3 live births), Baergen RN et al. [20] (2 IUGR/20 live births), and others [21, 22] (Table 4).

Among the histopathological evidence of MVM, perivillous and intervillous fibrin were the most common findings in the present study and in the studies done by Menter T et al. [15], Lu-Culligan A et al. [19], Baral G et al. [21], and many others [25] (Table 5). Infarction, which was a common feature among IUFD cases in the present study, was also reported in other similar studies [14, 25]. Though these features are commonly seen in placentas of COVID-19 positive mothers in various studies, these MVM features are consistently found associated with adverse outcomes in our study as well as others [14, 17].

Chorangiosis, a FVM feature which was a prominent observation in the current study, was also documented by Facchetti et al. [4] in a study of 101 cases. Evidence of increased avascular villi, which was also a noticeable component in the present research, was widely documented in many studies [24-27]. We noted fetal thrombotic vasculopathy in two (12%) cases, which was as high as 24.3% in a study done by Zhang P et al. [24]. Jak B et al. [23] also noticed similar pathology in his report of one case.

Various forms of inflammatory changes like chorioamnionitis, chronic villitis, and subchorionitis were seen in many research studies, as documented in a review by Gesaka SR et al. [25]. The present study exhibited chorioamnionitis in seven of the cases. Inflammatory changes like chorioamnionitis, intervillitis, and villitis/histiocytic intervillitis are associated with IUFD in our study as well as others [14, 17]. Prior to the SARS-CoV-2 pandemic, chronic histiocytic intervillositis was uncommon. On the other hand, a few studies observed minimal inflammatory changes [22, 28].

Examination using IHC revealed an interesting pattern where most of the infiltrating cells were CD68 positive, indicating a

histiocytic lineage. The present and many different studies also noticed this observation [14, 17, 25]. Sparse T cell (CD3+) and B cell (CD20+) infiltrations were observed in the current research as well as in other studies [25].

Conclusion

We conclude that COVID-19 can cause several placental lesions. Though no specific features pinpoint a characteristic diagnostic feature, there are increased rates of certain maternal and fetal vascular malperfusion features like increased perivillous and intervillous fibrin along with infarction. This suggests an increased propensity for thrombotic events leading to poor pregnancy outcomes. Inflammation predominantly by CD68 positive macrophages is also a dominant feature. Collectively, these findings indicate that increased antenatal surveillance for women diagnosed with SARS-CoV-2 is warranted to avoid adverse pregnancy outcomes. In any patient with confirmed coronavirus infection, antenatal surveillance like serial ultrasound with Doppler to assess placental development and arterial blood flow, serum levels of PAPP-A, PlGF, and D-dimer levels may help early detection of MVM and guide timely intervention and management of the pregnancy. These steps may help avoid adverse pregnancy outcomes.

Abbreviations:

SARS - Severe Acute Respiratory Syndrome
MERS - Middle-East Respiratory Syndrome
IUGR - Intrauterine Growth Retardation
IUFD - Intrauterine Fetal Death
IHC - Immunohistochemistry
MVM - Maternal Vascular Malperfusion
FVM - Fetal Vascular Malperfusion
TORCH - Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes Simplex Virus

Acknowledgement: Appreciation to all the patients who willingly participated in the study, as well as the technicians, colleagues, and postgraduate trainees for their continued support.

Declarations: RIMS, Imphal, India, under the Golden Jubilee Research Initiative.

Statement of informed consent: A patient information sheet was provided, and consequently, written informed consent was obtained from each patient.

Statement of human and animal rights: Ethical approval was obtained before the commencement of the study from the Institutional Ethics Committee, Research Ethics Board, RIMS, vide certification number A/206/REB/Prop(FP)/176/104/16/2022.

References

1. World Health Organization. Coronavirus disease (COVID-19) weekly epidemiological update. [Internet]. 2022 [cited 2024 Oct 5]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/covid_19_epi_update_167.pdf?sfvrsn=58f54395_2&download=true
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
3. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, 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.
4. Facchetti F, Bugatti M, Drera E, Tripodo C, Sartori E, Cancila V, 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.

5. Hosier H, Farhadian SF, Morotti RA, Deshmukh U, Lu-Culligan A, Campbell KH, et al. SARS–CoV-2 infection of the placenta. J Clin Invest. 2020;130(9):4947-53.
6. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-7.
7. Kulkarni VG, Sunilkumar KB, Nagaraj TS, Uddin Z, Ahmed I, Hwang K, et al. Maternal and fetal vascular lesions of malperfusion in the placentas associated with fetal and neonatal death: results of a prospective observational study. Am J Obstet Gynecol. 2021;225(6):660.e1.
8. Zur RL, McLaughlin K, Aalto L, Jiang Y, Huszti E, Parks WT, et al. Phenotypes of maternal vascular malperfusion placental pathology and adverse pregnancy outcomes: A retrospective cohort study. BJOG. 2024;131:1515-23.
9. Arts N, Schiffer V, Severens-Rijvers C, Bons J, Spaanderman M, Al-Nasiry S. Cumulative effect of maternal vascular malperfusion types in the placenta on adverse pregnancy outcomes. Placenta. 2022;129:43-50.
10. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med. 2016;140(7):698-713.
11. Singh N, Buckley T, Shertz W. Placental pathology in COVID-19: case series in a community hospital setting. Cureus. 2021;13(1)
12. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020;11(1):3572.
13. Hecht JL, Quade B, Deshpande V, Mino-Kenudson M, Ting DT, Desai N, 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):2092-103.
14. Corn M, Pham T, Kemp W. Adverse fetal outcomes and histopathology of placentas affected by COVID-19: A report of four cases. Cureus. 2023;15(8)
15. Menter T, Mertz KD, Jiang S, Chen H, Monod C, Tzankov A, et al. Placental pathology findings during and after SARS-CoV-2 infection: features of villitis and malperfusion. Pathobiology. 2021;88(1):69-77.
16. Sinaci S, Ocal DF, Seven B, Anuk AT, Besimoglu B, Keven MC, et al. Vertical transmission of SARS-CoV-2: A prospective cross-sectional study from a tertiary center. J Med Virol. 2021;93(10):5864-72.
17. Richtmann R, Torloni MR, Otani AR, Levi JE, Tobara MC, de Almeida Silva C, et al. Fetal deaths in pregnancies with SARS-CoV-2 infection in Brazil: a case series. Case Rep Womens Health. 2020;27
18. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-15.
19. Liu W, Wang Q, Zhang Q, Chen L, Chen J, Zhang B, et al. Coronavirus Disease 2019 (COVID-19) During Pregnancy: A Case Series. Preprints 2020;2020020373.
20. Baergen RN, Heller DS. Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol. 2020;23(3):177-80.
21. Baral G, Shrestha O, Baral RS. Thrombotic pathology in placenta of COVID positive pregnancy. J Nepal Health Res Counc. 2021;19(1):206-8.
22. Gao L, Ren J, Xu L, Ke X, Xiong L, Tian X, et al. Placental pathology of the third trimester pregnant women from COVID-19. Diagn Pathol. 2021;16:110.
23. Lu-Culligan A, Chavan AR, Vijayakumar P, Irshaid L, Courchaine EM, Milano KM, et al. Maternal respiratory SARS-CoV-2 infection in pregnancy is associated with a robust inflammatory response at the maternal-fetal interface. Med. 2021;2(5):591-610.
24. Zhang P, Salafia C, Heyman T, Lederman S, Dygulska B. Detection of severe acute respiratory syndrome coronavirus 2 in placentas with pathology and vertical transmission. Am J Obstet Gynecol MFM. 2020;2(4):100197.
25. Gesaka SR, Obimbo MM, Wanyoro A. Coronavirus disease 2019 and the placenta: A literature review. Placenta. 2022;126:209-23.
26. Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, et al. Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. Hum Reprod. 2021;36(4):899-906.
27. Jak B, Zanirati G, Rodrigues FV, Grahl M, Krimberg F, Pinzetta G, et al. Case report: placental maternal vascular malperfusion affecting late fetal development and multiorgan infection caused by SARS-CoV-2 in patient with PAI-1 4G/5G polymorphism. Front Med (Lausanne). 2021;8:624166.
28. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES, Goldstein JA. Placental pathology in covid-19. Am J Clin Pathol. 2020;154:23-32.