



Original Article

Correlation between placental histopathology and perinatal outcome in COVID-19

Devendra Arora^a, KS Rajmohan^b, Sanjay Singh^a, Vinod Nair^{a*}, Sanghita Barui^b, Madhusudan Dey^a, Abhijeet Kumar^a

^aDepartment of Obstetrics and Gynaecology, Base Hospital Delhi Cantt, New Delhi, India;
^bDepartment of Pathology, Base Hospital Delhi Cantt, New Delhi, India

ABSTRACT

Objectives: An alarming rate of adverse perinatal outcomes as well as maternal deaths has been reported worldwide during this pandemic. It would be prudent to start thinking on the lines of acute or chronic intrauterine fetal hypoxia due to placental microvascular pathology or villitis caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. Autopsy studies of deceased patients with severe COVID-19 have revealed the presence of diffuse pulmonary alveolar damage, thrombosis, and microvascular injuries. It is expected that similar pathological features such as microvascular injuries could be found in the placenta of infected pregnant women. **Materials and Methods:** Placentas of singleton pregnancies from 42 SARS-CoV-2 positive mothers delivered at term were submitted for histopathological examination. Those with multifetal gestation, hypertensive disorder, fetal growth restriction, structural or chromosomal anomalies in the fetus, thrombophilia, prolonged prelabor rupture of membranes, and placenta accreta spectrum were excluded from the study. Histopathological examination was done by two pathologists independently and only those results concurred by both were reported. Histopathological features and corresponding neonatal outcome were analyzed. **Results:** Reports of 42 placentas from patients with SARS-CoV-2, delivered at term (37–40 weeks) were analyzed in our study. Features of maternal vascular malperfusion (MVM) were present in 45% ($n = 19$) cases. Features of fetal vascular malperfusion (FVM) were present in 23.8% ($n = 10$) cases. There were 47.6% ($n = 20$) cases showing at least one feature of acute inflammatory pathology (AIP) and 42.8% ($n = 18$) showing features of chronic inflammatory pathology (CIP). Neonatal respiratory distress syndrome was found in 19% ($n = 8$) of the neonates. Correspondingly, nearly all placentas ($n = 7$) of these neonates showed features of MVM, FVM, AIP and CIP. There was no maternal or neonatal mortality in our study group. **Conclusion:** The main findings of our study include maternal as well as fetal vascular malperfusion and placental inflammatory pathology. These findings provide an outline for better understanding of etiological factors and pathogenesis of adverse perinatal outcomes in SARS-CoV-2 infection.

KEYWORDS: COVID-19, Histopathology, Perinatal outcome, Placenta, Pregnancy

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INTRODUCTION

Coronaviruses are enveloped single-stranded RNA viruses that infect both humans and animals [1]. Human coronaviruses cause a wide spectrum of respiratory illnesses ranging from mild upper respiratory tract infections to severe pneumonia [2-4]. Severe acute respiratory syndrome-coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019 are the three clinically important Coronaviruses which have caused serious respiratory illness and

death in humans [5]. The primary target of SARS-CoV is ciliated epithelial cells. SARS-CoV binds to the cells via angiotensin converting enzyme 2 receptor [6]. Various human tissues that express ACE-2 receptors are cardiovascular, gastrointestinal, adipose, pulmonary and renal tissues. In addition to these, human placenta also expresses ACE-2 receptors [7].

*Address for correspondence: Dr. Vinod Nair,

Department of Obstetrics and Gynaecology, Base Hospital Delhi Cantt, Hospital Road, Chanan Singh Park, Delhi Cantonment, New Delhi, India.
 E-mail: nair.vinod19@gmail.com

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The coronavirus disease-19 (COVID-19) in pregnant women is of particular interest to obstetricians worldwide. There is a growing evidence to suggest human placenta as an immune organ [8]. Placental immune response to various maternal infections and their transplacental transmission are of utmost clinicopathological significance in modern medicine. Several case series and meta-analyses have concluded that SARS infection during pregnancy was associated with severe maternal infection, increased risk of maternal death, and spontaneous abortion [9-15]. Meta-analysis of case reports and case series on vertical transmission of SARS-CoV-2 have revealed negative polymerase chain reaction (PCR) results for SARS-CoV-2 in the neonate, placenta, cord blood, and vaginal secretions in majority of cases [16]. Several studies have already been conducted to find out the pathological features of placentas of pregnant women with COVID-19. Acute or chronic inflammatory changes in these placentas were rarely found. However, microvascular changes and maternal vascular malperfusions (MVM) were almost a constant finding [1,17,18].

An alarming rate of adverse perinatal outcomes as well as maternal deaths has been reported worldwide during this pandemic. Though many of these adverse pregnancy outcomes have been attributed to a collapsed health care system due to a sudden peak in COVID-19 cases, it would be prudent to start thinking on the lines of acute or chronic intrauterine fetal hypoxia due to placental microvascular pathology or villitis caused by SARS-CoV-2 infection. Viral infections during pregnancy have a wide spectrum of placental pathology [19]. Numerous viruses cause villitis and spontaneous abortions [19-21]. Autopsy studies of deceased patients with severe COVID-19 have revealed the presence of diffuse pulmonary alveolar damage in nearly all cases [22-26]. Thrombosis and microvascular injuries were the other significant findings. It is expected that similar pathological features such as microvascular injuries could be found in the placenta of infected pregnant women.

MATERIALS AND METHODS

The study was conducted from March 2021 to May 2021 at a 1000 bedded tertiary care center which is also a designated COVID hospital. The study was approved by the Institutional Ethics Committee of Base Hospital and Army College of Medical Sciences, Delhi Cantt, vide their letter No. IEC/01/2021/02 dated 18 Mar 2021. All patients with singleton pregnancy at term who have been tested positive for SARS-CoV-2 were included in the study. Those with multifetal gestation, hypertensive disorder, fetal growth restriction (FGR), structural or chromosomal anomalies in the fetus, thrombophilia, prolonged prelabour rupture of membranes, and placenta accreta spectrum were excluded from the study. Written informed consent was taken from each participant. Testing was done by Cartridge Based Nucleic Acid Amplification Test using GeneXpert Dx Xpert Xpress SARS-CoV-2 (Cepheid) system approved by United States-Food and Drug Administration for use under an emergency use authorization (available at <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/>

emergency-use-authorizations). The analytical sensitivity and specificity are reported by the manufacturer as 95.65% (95% confidence interval [CI]: 88.4%–99.6%) and 97.72% (95% CI: 85.2%–98.8%) respectively. Positive SARS-CoV-2 test was considered the foremost criterion for submission of placentas for pathological examination.

In an earlier similar type of study, Shanes *et al.* (2020) had demonstrated that third trimester placentas of SARS-CoV-2 positive mothers were significantly more likely to show at least one feature of maternal vascular malperfusion (MVM), in which MVM was present in 12/15 cases, significantly higher than historical controls (59/215, $P = 0.001$) [17]. Assuming that similar results could be obtained in our study, a minimum number of 26 patients were considered sufficient enough to deduct statistical significance. However, in order to bring out more substantial evidence, it was decided to recruit 50 patients in the study. Forty-two ($n = 42$) third trimester placentas of singleton term delivery were finally submitted for histopathological examination from women with COVID-19, delivered between March 2021 and May 2021 as depicted Figure 1.

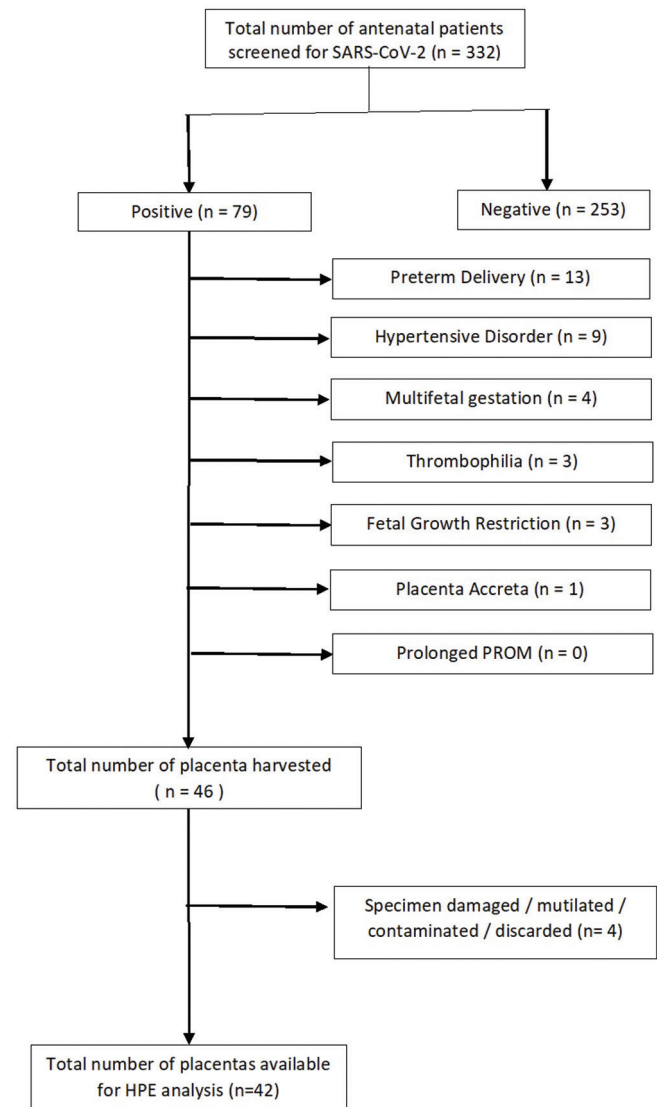


Figure 1: Flowchart depicting patient enrolment

All placentas were examined clinically after delivery before putting into fixatives. Photographs of the maternal and fetal surfaces, measurements, and trimmed weight were taken. The placentas were kept in 10% buffered formalin for the next 48 h, for fixation as well as viral inactivation. Examination of the cut surfaces and sectioning was done after adequate fixation. Sections submitted included 2 of umbilical cord, 2 of membrane rolls, 3 sections from placental parenchyma including 2 full-thickness sections, and representative sampling of any lesions present. Sections underwent routine processing, embedding, sectioning at 4 μ m, and staining with hematoxylin and eosin (H and E).

Histologic sections were thoroughly examined to look for features of maternal vascular malperfusions (MVM), fetal vascular malperfusions (FVM), acute or chronic inflammatory pathology (AIP/CIP), and any other relevant findings (microscopic accreta, villous edema, increased perivillous fibrin, intervillous thrombus, membranes with hemorrhage, abnormal or injured maternal vessels, and intervillous thrombi). H and E-stained sections were examined and reported independently by two pathologists and only those findings for which both the pathologists concurred unanimously were reported. Pathological findings were classified according to the current Amsterdam Placental Workshop Group Consensus Statement [27].

Those patients who had respiratory compromise requiring continuous respiratory support underwent cesarean delivery. General anesthesia was not administered in any of the cases. All deliveries were attended by the neonatologist of the hospital. Those neonates requiring continued respiratory support were immediately shifted to the neonatal intensive care unit (NICU) with a diagnosis of respiratory distress syndrome (RDS).

RESULTS

Majority of the pregnant women who were tested positive for SARS-CoV-2 were either asymptomatic or had mild symptoms. Twelve patients (28.57%) had breathlessness requiring respiratory support. The detailed symptomatology, mode of delivery, placental histopathological features, and corresponding perinatal outcome are expressed in Table 1.

Reports of 42 placentas from patients with SARS-CoV-2 delivered at term (37–40 weeks) were analyzed. Total 8 of 42 placentas weighted above 90th percentile and 3 weighted below 10th percentile for term gestational age. One umbilical cord revealed 4 vessels (2 arteries and 2 veins). Three umbilical cords were hyper coiled [depicted in Figure 2a] and one cord was very thin with narrow cord diameter (<8 mm). Marginal cord insertion was noted in 2 cases. One placenta was found meconium stained [depicted in Figure 2b].

Features of MVM were present in 45% ($n = 19$) cases. Features included central ($n = 8$)/peripheral ($n = 3$), villous infarctions/necrosis, increased syncytial knots ($n = 5$) and accelerated villous maturation ($n = 3$). Villous agglutination was seen in one case ($n = 1$) and retroplacental hematoma in two cases ($n = 2$). Decidual arteriopathy occurred in 30.9% ($n = 13$) cases in the form of mural hypertrophy of membrane arterioles ($n = 10$) and absent spiral artery remodeling ($n = 3$). However, no atherosclerosis or fibrinoid necrosis

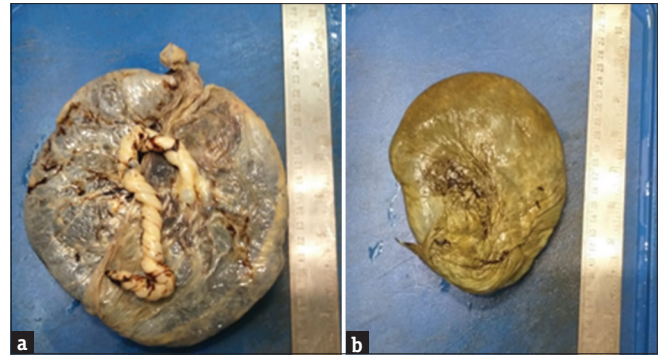


Figure 2: (a) Hypercoiling of umbilical cord; (b) meconium-stained placenta

of maternal vessels was noted. Microscopic features of MVM are depicted in Figure 3. Peripheral infarctions, decidual arteriopathy with mural hypertrophy were common findings in our cases. Features of FVM were present in 23.8% ($n = 10$) cases and one showed clustered avascular villi. One case of mural fibrin and one case of mural hypertrophy of fetal vessels were also identified. Four placentas showed chorangiosis. Microscopic features of FVM are depicted in Figure 4.

Rates of both AIP and CIP were substantially increased in COVID-19 cases in the form of subchorionitis, chorioamnionitis, villitis/intervillositis and deciduitis. There were 47.6% ($n = 20$) cases showing at least one feature of AIP and 42.8% ($n = 18$) showing features of CIP. Varying degree of villous edema was found in most of the cases; 73.8% ($n = 31$). Perivillous fibrin deposition was seen in 40.5% ($n = 17$) cases. Microscopic features of inflammatory pathology are depicted in Figure 5.

Neonatal RDS was found in 19% ($n = 8$) of the neonates. Correspondingly, nearly all placentas ($n = 7$) of these neonates showed features of MVM, FVM, AIP, and CIP. Placenta of the remaining one neonate with RDS showed features suggestive of villous edema. There was no maternal or neonatal mortality in our study group.

DISCUSSION

Significant advances have been made by the medical fraternity in understanding pathological spectrum of SARS-CoV-2 infection and its various systemic effects. However, some lacunae still remain in understanding placental pathology of SARS-CoV-2 infection in pregnant women. In a systematic review and meta-analysis of 42 studies involving 4,38,548 pregnant women, Wei *et al.* have demonstrated that COVID-19 was strongly associated with preeclampsia (odds ratio [OR] 4.16, 95% CI 1.55–11.15), preterm birth (OR 4.29, 95% CI 2.41–7.63), gestational diabetes (OR 1.99, 95% CI 1.09–3.64) and low birth weight (OR 1.89, 95% CI 1.14–3.12) [28]. In another systematic review of 66 studies by Abdel Massih *et al.*, involving 1787 SARS-CoV-2 positive mother-infant pairs, it was concluded that even though vertical transmission is rare, there is an increased risk of placental insufficiency due to prothrombotic tendency in COVID-19 infection. It was also revealed that 20% of these cases had intrauterine hypoxia due to placental abnormalities suggestive of placental vaso-occlusive involvement [29].

Table 1: Maternal symptoms, mode of delivery, placental histopathological features and corresponding neonatal outcome

Case number	POG (weeks + days)	Symptoms and SpO2 on room air	Mode of delivery	Indication for LSCS	Birth-weight (kg)	Placental weight (kg)	Placental histopathology (significant findings)	NICU admission for RDS
1	37+4	Asymptomatic SpO2=98%	VD	-	3.2	0.54	NAD	No
2	39+0	Fever, dry cough SpO2=96%	VD	-	2.6	0.35	NAD	No
3	38+3	Asymptomatic SpO2=100%	VD	-	3.4	0.53	Villous edema	No
4	38+6	Fever, dry cough SpO2=94%	VD	-	3.0	0.48	NAD	No
5	37+3	Asymptomatic SpO2=97%	LSCS	Fetal distress	2.4	0.40	MVM, FVM, AIP Villous edema	Yes
6	38+6	Asymptomatic SpO2=99%	VD	-	2.8	0.45	Villous edema	No
7	37+4	Breathlessness SpO2=82%	LSCS	Maternal respiratory compromise	2.9	0.50	MVM, FVM, AIP, CIP Villous edema	Yes
8	39+5	Breathlessness SpO2=86%	LSCS	Maternal respiratory compromise	3.4	0.51	MVM, AIP, CIP	No
9	39+1	Asymptomatic SpO2=99%	VD	-	3.6	0.60	NAD	No
10	37+3	Asymptomatic SpO2=96%	VD	-	3.1	0.48	NAD	No
11	38+2	Breathlessness SpO2=89%	LSCS	Maternal respiratory compromise	2.8	0.45	MVM, FVM, CIP Villous edema	No
12	38+0	Breathlessness SpO2=92%	LSCS	Previous LSCS	3.7	0.72	MVM, AIP, CIP Villous edema	No
13	39+6	Breathlessness SpO2=90%	LSCS	Malpresentation	3.5	0.70	MVM, FVM, AIP, CIP Villous edema	No
14	38+5	Fever, dry cough SpO2=94%	LSCS	Previous LSCS	2.5	0.30	AIP, CIP Villous edema	No
15	38+3	Breathlessness SpO2=88%	LSCS	Maternal respiratory compromise	2.7	0.45	MVM, FVM, AIP, CIP Villous edema	Yes
16	37+5	Asymptomatic SpO2=97%	VD	-	2.8	0.45	Villous edema	No
17	37+6	Asymptomatic SpO2=100%	VD	-	2.7	0.45	Villous edema	No
18	39+2	Asymptomatic SpO2=97%	VD	-	2.9	0.50	AIP, CIP Villous edema	No
19	37+4	Asymptomatic SpO2=96%	VD	-	3.2	0.70	Villous edema	No
20	38+5	Asymptomatic SpO2=98%	VD	-	3.4	0.55	Villous edema	No
21	37+3	Asymptomatic SpO2=99%	LSCS	Previous LSCS	2.8	0.46	Villous edema	No
22	38+4	Asymptomatic SpO2=98%	LSCS	Previous LSCS	3.3	0.50	NAD	No
23	38+5	Breathlessness SpO2=90%	VD	-	2.9	0.48	MVM, AIP Villous edema	No
24	39+2	Fever, dry cough SpO2=94%	LSCS	Previous LSCS	3.0	0.50	NAD	No
25	37+6	Fever, dry cough SpO2=95%	LSCS	Fetal distress, MSL	2.6	0.45	MVM, FVM, AIP Villous edema	No

Contd...

Table 1: Contd...

Case number	POG (weeks + days)	Symptoms and SpO ₂ on room air	Mode of delivery	Indication for LSCS	Birth-weight (kg)	Placental weight (kg)	Placental histopathology (significant findings)	NICU admission for RDS
26	37+5	Asymptomatic SpO ₂ =98%	VD	-	2.8	0.45	NAD	No
27	39+2	Breathlessness SpO ₂ =84%	LSCS	Fetal distress, maternal respiratory compromise	2.9	0.35	MVM, FVM, CIP Villous edema	Yes
28	38+4	Fever, dry cough SpO ₂ =94%	LSCS	Malpresentation	3.2	0.65	MVM, AIP Villous edema	No
29	38+3	Asymptomatic SpO ₂ =97%	VD	-	2.9	0.60	Villous edema	No
30	37+4	Fever, dry cough SpO ₂ =94%	LSCS	Previous LSCS	2.8	0.47	MVM, AIP, CIP Villous edema	No
31	38+2	Fever, dry cough SpO ₂ =95%	LSCS	Previous LSCS	3.5	0.70	MVM, AIP, CIP Villous edema	No
32	39+2	Fever, dry cough SpO ₂ =96%	VD	-	2.7	0.45	MVM, AIP, CIP Villous edema	No
33	39+0	Asymptomatic SpO ₂ =98%	VD	-	2.8	0.44	Villous edema	Yes
34	37+0	Breathlessness SpO ₂ =92%	LSCS	Previous LSCS	3.0	0.49	MVM, AIP, CIP Villous edema	No
35	37+2	Asymptomatic SpO ₂ =98%	VD	-	3.1	0.50	Villous edema	No
36	37+1	Breathlessness SpO ₂ =89%	LSCS	Maternal respiratory compromise Fetal distress	2.8	0.46	MVM, FVM, AIP, CIP Villous edema	Yes
37	38+6	Asymptomatic SpO ₂ =98%	LSCS	Fetal distress	2.6	0.45	FVM, AIP, CIP Villous edema	No
38	38+5	Breathlessness SpO ₂ =82%	LSCS	Maternal respiratory compromise	3.1	0.48	MVM, AIP, CIP Villous edema	No
39	39+0	Asymptomatic SpO ₂ =98%	VD	-	2.9	0.47	NAD	No
40	38+5	Fever, dry cough SpO ₂ =94%	VD	-	2.8	0.46	NAD	No
41	39+0	Breathlessness SpO ₂ =82%	LSCS	Maternal respiratory compromise	2.5	0.41	MVM, FVM, AIP, CIP Villous edema	Yes
42	37+2	Fever, dry cough SpO ₂ =94%	VD	-	3.0	0.65	MVM, AIP, CIP Villous edema	Yes

SpO₂: Oxygen saturation, POG: Period of gestation, LSCS: Lower segment caesarean section, VD: Vaginal delivery, NICU: Neonatal intensive care unit, RDS: Respiratory distress syndrome, MVM: Maternal vascular malperfusion, FVM: Fetal vascular malperfusion, AIP: Acute inflammatory pathology, CIP: Chronic inflammatory pathology, NAD = No abnormality detected, MSL = Meconium stained liquor

The placenta is a unique organ that possesses dual blood circulations, which provide oxygen and nutrients to the fetus. The unimpeded flow of properly oxygenated maternal and fetal blood is critical to placental function. Pathologic conditions affecting the maternal vasculature and circulation can cause significant adverse effects to the fetus. These conditions associated with pathologic maternal blood flow are currently known under the terminology: Maternal vascular malperfusion (MVM), as defined in the Amsterdam consensus [27]. It is already known that MVM is a common finding in pregnancies complicated by preeclampsia and FGR [29-32].

Gross findings of MVM include placental hypoplasia, placental infarction, and retroplacental hemorrhage. Placental

hypoplasia is defined as a placental weight below the 10th percentile expected for gestational age and/or a thin umbilical cord, defined as width below the 10th percentile for gestational age or <8 mm at term [33,34]. In our study, 3 placentas weighed below 10th percentile for the gestational age and one umbilical cord measured <8 mm in diameter. In a similar study by Shanes *et al.*, it was found that 5 out of 15 placentas were hypoplastic [17]. In the same study, researchers have found that 80% ($n = 12$) placentas had one or more features suggestive of MVM. These features include central and peripheral villous infarction, accelerated villous maturation and villous agglutination. Similar results have been obtained in our study.

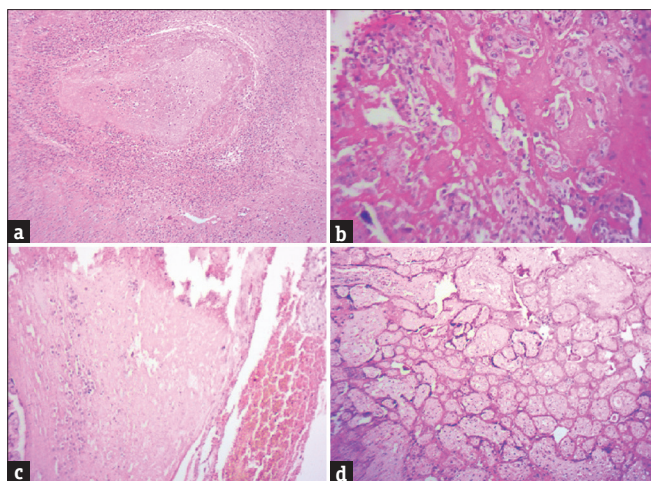


Figure 3: (a) Intervillous thrombus-10X; (b) Increased perivillous fibrin-20X; (c) retroplacental haematoma-10X; (d) Villous agglutination-4X

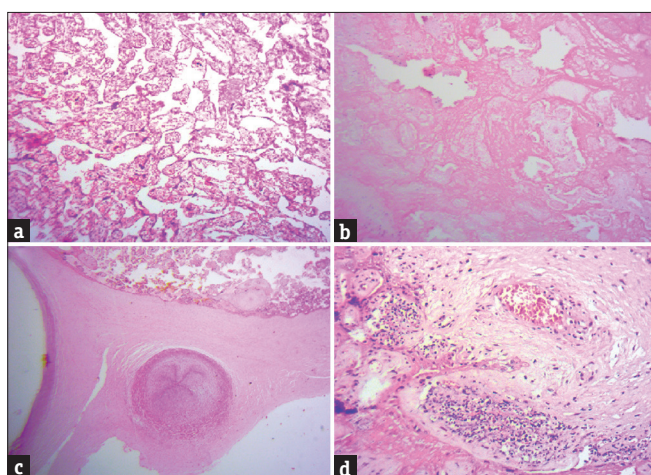


Figure 4: (a) Chorangiomas-10X; (b) Necrotic ghost villi -10X; (c) mural hypertrophy of fetal vessels-20X; (d) acute vasculitis, mural fibrin-10X

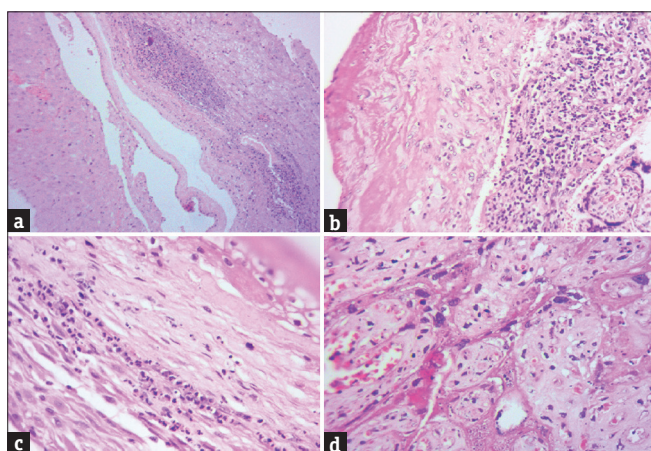


Figure 5: (a) Acute chorioamnionitis-10X; (b) chronic deciduitis-20X (c) Acute deciduitis-40X; (d) Villitis, Intervillositis-20X

FVM is a term applied to a group of placental lesions indicating reduced or absent perfusion of the villous parenchyma by the fetus. The most common etiology of malperfusion is umbilical cord obstruction leading to stasis,

ischemia, and in some cases thrombosis. Other contributing factors may include maternal diabetes, fetal cardiac insufficiency or hyperviscosity, and inherited or acquired thrombophilias. Severe or high-grade FVM is an important risk factor for adverse pregnancy outcomes including FGR, fetal CNS injury, and stillbirth [35]. FVM is diagnosed by the presence of vascular lesions in the fetal vessels in the placenta and the resultant changes in the downstream villi [36]. In our study, features of FVM were present in 23.8% ($n = 10$) placental specimens. Sharps *et al.*, in a structured review have brought out features or diagnoses of FVM in 53 cases (35.3%) of placentas examined, 95% CI 27.7–42.9%) by 6 studies [37].

Even though the placental inflammatory response to SARS-CoV-2 is usually expected, most of the studies could not prove this on histopathological examination [16-18]. In our study, 47.6% ($n = 20$) cases showed acute inflammation and 42.8% ($n = 18$) showed features of chronic inflammation. Similar evidence was revealed by Sharps *et al.* in “a structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection” (villitis 8.7% cases, intervillitis 5.3% of cases, and chorioamnionitis 6% of cases) [37].

In our study, all the neonates were tested negative for SARS-CoV-2 reverse transcription-PCR. There were 8 neonates requiring NICU admission for management of RDS. There was no neonatal or maternal mortality in our study. These findings are in conjunction with other reviews and studies conducted by Sharps *et al.* and Blasco Santana *et al.* [37,38].

CONCLUSION

Vertical transmission of SARS-CoV-2 from infected pregnant mother has always been a point of discussion since the beginning of COVID-19 pandemic. Numerous studies have already been conducted to bring out evidence regarding placental pathology in SARS-CoV-2 infection and resultant vertical transmission of the disease to the fetus. However, concrete evidence in this regard is still lacking. Interestingly, in most of the studies, only miniscule number of newborns has been tested positive for SARS-CoV-2, despite the high positivity rate of placentas. Further studies are required to understand the immunological response and barrier function of the placenta in response to SARS-CoV-2 infection. Several studies depicting histopathological examination findings of placenta in SARS-CoV-2 infection are available on literature search. In almost all of these studies, the infection to delivery interval was very short. Hence, chronic inflammation of placenta and resultant pathological effect could not be studied. Further, since these studies are being conducted during a pandemic, comparison with appropriate controls is nearly impossible. Here, we have reported histopathological examination findings of 42 placentas from SARS-CoV2 positive pregnant women in an Indian scenario. The main findings of our study include maternal as well as fetal vascular malperfusions and placental inflammatory pathology. These findings provide an outline for a better understanding of etiological factors and

pathogenesis of adverse perinatal outcomes in SARS-CoV-2 infection. Our study is single institutional and is limited by its small sample size and lack of comparison with appropriate controls. We recommend larger multicentric studies with appropriate controls in the near future for generalization of our findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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