



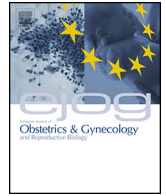
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COVID-19 as an independent risk factor for subclinical placental dysfunction

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ABSTRACT

Background: The pandemic of the severe acute respiratory distress syndrome-associated Coronavirus-2 (SARS-CoV-2) has affected millions around the world. In pregnancy the dangers to the mother and fetus are still being explored. SARS-CoV2 can potentially compromise maternal and neonatal outcomes and this may be dependent on the pregnancy stage during which the infection occurs.

Objective: The present study was done to find the histopathological alterations in the placenta of SARS-CoV-2 positive pregnancies with either no symptoms or mild coronavirus disease (COVID)-19 related symptoms and its association with neonatal outcomes.

Study design: This was a prospective analytical study. Twenty seven asymptomatic or mildly symptomatic SARS-CoV-2 positive pregnant women with a singleton pregnancy delivered between 1st July 2020 and 15th September 2020, were included as cases. An equal number of SARS-CoV-2 negative singleton pregnancies matched for maternal and gestational age during the same period were included as controls. After delivery the histopathological examination of the placenta of these women was done and the findings recorded on a predesigned proforma based on the Amsterdam consensus criteria for evidence of maternal and fetal vascular malperfusion changes.

Results: The baseline characteristics were comparable between the cases and controls. The following features of maternal vascular malperfusion (MVM) were significantly higher in the placentae of COVID-19 positive pregnancies: retroplacental hematomas (RPH), accelerated villous maturation (AVM), distal villous hyperplasia (DVH), atherosclerosis, fibrinoid necrosis, mural hypertrophy of membrane arterioles (MHMA), vessel ectasia and persistence of intramural endovascular trophoblast (PIEVT). Fetal vascular malperfusion (FVM) significantly associated with the positive pregnancies were chorioangiomas, thrombosis of the fetal chorionic plate (TFCP), intramural fibrin deposition (IMFD) and vascular ectasia. Additionally, perivillous fibrin deposition was also significantly higher in the placentae of cases.

The percentage of spontaneously delivered women was comparable in the two groups. The sex and weight of the newborn and the number of live births were comparable between the two groups.

Conclusions: Asymptomatic or mildly symptomatic SARS-CoV-2 positive pregnant women, with otherwise uncomplicated pregnancies, show evidence of placental injury at a microscopic level. Similar findings have been demonstrated in other studies too. This placental injury apparently does not lead to poor pregnancy outcomes. The extent of this injury in symptomatic cases of COVID-19 pregnancies and its consequences on the outcomes need to be analysed.

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Introduction

The pandemic of the severe acute respiratory distress syndrome-associated Coronavirus-2 (SARS-CoV-2), the etiologic agent of Coronavirus disease 2019 (COVID-19), emerged in December 2019 in Wuhan, China [1]. The pandemic has infected more than 40 million people worldwide till date and left more than a million are dead. Previous Coronavirus pandemics like the SARS-

CoV and the Middle East Respiratory syndrome Coronavirus (MERS-CoV) were associated with poor maternal and fetal outcomes [2]. However, the dangers that this pandemic poses to the pregnant women and their newborn babies are still being explored. In a recent systematic review, Allotey et al. concluded that COVID-19 infection manifested with none or minimal symptoms in most pregnant women, but they were also more likely to need intensive care treatment for COVID-19. Pre-existing morbidities, advanced maternal age and high body mass index were factors attributed to increase in disease severity [3]. Histopathologic examination (HPE) of the placental tissue can provide significant information regarding the health of both mother and the newborn and provide clues to the pathophysiology of materno-fetal disease. SARS-CoV2 can potentially compromise maternal and neonatal outcomes and this may be dependent on the pregnancy stage during which the infection occurs as has been observed with other SARS-CoV infection. Potential of placental and fetal damage, during the first and second trimester of pregnancy due to COVID-19 exists and inflammatory mediators may play a role in this by altering placental permeability [4]. Placental alterations have been described in other viral infections such as Cytomegalovirus, Zika virus and Dengue virus [5]. The present study explores the histopathological changes in the placenta in SARS-CoV-2 positive pregnancies with no symptoms or mild symptoms and their association with neonatal outcomes.

Materials and methods

This was a prospective analytical study conducted at the Lady Hardinge Medical College and associated Hospitals, New Delhi, which is a tertiary level referral centre in North India that caters to approximately 11,000–12,000 deliveries per year.

In our hospital all pregnant women requiring admission are tested for the novel Coronavirus with nasopharyngeal reverse transcriptase polymerase chain reaction (NP-RT-PCR). All consecutive asymptomatic and mildly symptomatic pregnant women with a singleton pregnancy delivered between 1st July 2020 and 15th September 2020, where the mother tested positive for the SARS-CoV-2 infection, were included as cases. All pregnant women diagnosed with and/or suspected to have uteroplacental insufficiency like fetal growth restriction, hypertensive disorders of pregnancy and diabetes mellitus were excluded from the study. An equal number of SARS-CoV-2 negative singleton pregnancies matched for maternal and gestational age who delivered during this period were included as controls.

After delivery, the placenta of these women was fixed in 10 % buffered formalin for histopathological examination (HPE). A total of 8 sections were taken from the placenta: 2 from the maternal surface, 2 from the fetal surface, 2 full thickness sections and one section each from the membranes and umbilical cord. The sections were stained with hematoxylin and eosin (H&E) after routine processing. The histopathological examination was done by two pathologists. The findings were recorded on predesigned proforma based on the Amsterdam consensus criteria for evidence of maternal and fetal vascular malperfusion changes and other associated findings [6].

The data was analysed by using the software Statistical Package for the Social Sciences (SPSS) version 18.0 [Chicago: SPSS Inc.]. The frequency along with percentages are given for categorical variables. Mean with standard deviation was used for continuous data. Independent *t*-test, chi-square test and Fisher's exact test was used to test the association. The measurement of risk was done by measuring the relative risk. A *p*-value of less than 0.05 was considered as statistically significant.

The study was approved by the Institutional Ethics Committee. (LHMC/IEC/2020/53)

Results

A total of 27 SARS-CoV-2 positive pregnant women and an equal number of age and gestational age matched controls were included in the study. Fever was the commonest symptom in the SARS-CoV-2 positive pregnant women. None of the cases had any respiratory symptom. The percentage of spontaneously delivered women was comparable in the two groups. The sex and weight of the newborn were comparable between the two groups. (Table 1) Anemia was present in approximately 25 % pregnant women in each group. There were no cases of prelabour rupture of membranes (PROM) and two cases with antepartum hemorrhage (APH) in the SARS-CoV-2 positive pregnancies compared to four cases of PROM and three cases of APH in controls respectively. There were four stillbirths in the cases and six in the control group. (Table 1)

In terms of the changes in the placenta we found that following features of maternal vascular malperfusion (MVM) were significantly higher in the placenta of SARS-CoV-2 positive pregnancies: retroplacental hematomas (RPH) [(*p* = 0.001); relative risk (RR) = 2.40(1.57–3.66)], accelerated villous maturation (AVM) [(*p* = 0.001); RR = 2.41(1.51–3.84)], distal villous hyperplasia (DVH) [(*p* < 0.0001); RR = 2.67(1.52–4.67)], atherosclerosis/fibrinoid necrosis

Table 1
Baseline characteristics of study participants.

Variables	Cases(n = 27)	Controls(n = 27)	p-value
Age (in year)	26.6±4.6	24.8±4.9	NS*
Gestational age (in days)	265.0±18.1	268.48±15.9	NS*
Birth weight of baby (in grams)	2568.1±559.4	2658.5±558.1	NS*
Gravida			
G1	12(44.4)	7(25.9)	NS**
G2	9(33.3)	11(40.7)	
≥G3	6(22.3)	9(33.4)	
Parity			
P0	14(51.9)	11(40.7)	
P1	10(37.0)	10(37.0)	NS**
≥P2	3(11.1)	3(22.3)	
Risk factors			
None	25(92.6)	20(74.1)	NS**
Per-vaginum leaking	0(0.0)	4(14.8)	0.037***
Antepartum hemorrhage	2(7.4)	3(11.1)	NS**
Fever	9(33.3)	1(3.7)	0.005***
Respiratory symptoms	0(0.0)	0(0.0)	–
Anemia	8(29.6)	7(25.9)	NS**
Mode of delivery			
Vaginal delivery	18(66.7)	23(85.2)	NS**
Caesarean section	9(33.3)	4(14.8)	
Color of liquor			
Blood stained	1(3.7)	0(0.0)	NS**
Clear	22(81.5)	18(66.7)	
Meconium stained	4(14.8)	9(33.3)	
Neonatal APGAR score (at 5 min)			
0	4(14.8)	6(22.2)	NS**
8	11(40.8)	7(25.9)	
9	7(25.9)	12(44.5)	
10	5(18.5)	2(7.4)	
Maternal Blood group			
A+	6(22.2)	11(40.8)	NS**
B+	10(37.0)	10(37.0)	
AB+	3(11.1)	0(0.0)	
O+	8(29.7)	5(18.5)	
B-	0(0.0)	1(3.7)	
Birth outcome			
Live birth	23(85.2)	21(77.8)	NS**
Still born	4(14.8)	6(22.2)	
Sex of baby			
Male	16(59.3)	12(44.4)	NS**
Female	11(40.7)	15(55.6)	

Categorical variable are presented as number(%) and continuous data as mean ± standard deviation.

* : independent *t*-test.

** : chi square test.

*** : Fisher's exact test.

($p = 0.010$), mural hypertrophy of membrane arterioles (MHMA) [($p < 0.0001$); RR = 4.36(2.10–9.09)], vessel ectasia ($p = 0.002$) (Table 2) (Fig. 1).

The following features of fetal vascular malperfusion (FVM) were significantly associated with the SARS-CoV-2 positive pregnancies: chorioangiomas [($p = 0.001$); RR = 2.41(1.51–3.84)], intramural fibrin deposition (IMFD) ($p = 0.023$) and vascular ectasia [($p = 0.004$); RR = 2.16(1.38–3.38)]. Additionally, perivillous fibrin deposition was also significantly higher in the placental histopathology of cases [($p < 0.0001$); RR = 4.95(1.98–12.34)] (Table 2) (Fig. 1).

Additional features of MVM [villous infarcts (VI), persistence of intramural endovascular trophoblast (PIEVT), persistent muscularization of basal plate arterioles (PMBPA), basal decidual vessel thrombosis (BDVT)], FVM [avascular villi (AV), thrombosis of the fetal chorionic plate (TFCP) and villous stromal vascular karyorrhexis (VSVK)] and other features [intravillous fibrin deposition (IVFD), maternal floor infarcts (MFI), chorioamnionitis and villous agglutination (VA)] were found more in the SARS-CoV-2 positive pregnancies but the difference was not statistically significant as compared to the controls (Table 2) (Fig. 1).

Discussion

In our study we found that the histopathological evidence of maternal and fetal vascular malperfusion were significantly higher in the placental tissues of the cases in comparison to controls. The presence of VI and RPH are indicative of placental hypoperfusion and are common findings in placenta of pre-eclamptic pregnancies [7]. Microthrombi, fibrin deposition and occlusion of the placental spiral arteries can lead to placental infarcts. In our study we found a significantly higher proportion of cases with RPH. Malperfusion can lead to changes such as AVM and subsequent DVH due to a poorly developed distal villous tree [8]. Both these findings were significantly higher in cases. Decidual arteriopathy is another histopathological characteristic of MVM and comprises of acute

atherosis/fibrinoid necrosis, BDVT, MHMA and PIEVT. Abnormal remodelling of spiral arteries after persistent hypoxic injury results in atherosclerosis (necrosis) [9]. In the present series too, the placental samples of the cases showed significantly greater atherosclerosis and MHMA indicating that decidual arteriopathy was more in the cases. The presence of maternal vascular ectasia was more in the cases and is caused by a dilatation of the vascular diameter secondary to increased intravascular pressure and can be secondary to vascular remodelling following ischaemia [10].

Fetal vascular thrombi develop due to various combinations of three risk factors (Virchow's triad) – stasis, hypercoagulability, and endothelial or vessel wall damage. Degeneration and loss of capillaries can occur secondary to thrombosis in the chorionic plate. Acute thrombosis can lead to the villi becoming avascular and the presence of fibrosis indicates chronicity of the process [11]. Chorioangiomas is a result of the initial ischaemic phase and consequent karyorrhexis of fetal endothelium with resultant capillary wall disruption, spillage of necrotic cell fragments into the villous stroma with resultant degeneration. Vascular ectasia can occur secondary to increased intraluminal pressure and degeneration [10]. The significant association of chorioangiomas, IMFD and vascular ectasia of fetal vessels with SARS-CoV-2 positive pregnancies is indicative of the evidence of FVM in the placenta of the affected pregnancies.

Whereas small amounts of fibrin are commonly scattered throughout the normal placenta, inadequate placental blood flow can result in focal necrosis and widespread fibrin deposition. Diffusely increased amounts of intravillous and perivillous fibrin involving stem and terminal villi and large villi may impair gas exchange. MFI in placenta is a result of the fibrinoid material in the maternal surface and intervillous spaces of the placenta and is known to cause growth restriction. VA is a manifestation of villous damage secondary to hypoxia to the villi [12]. Chorioamnionitis can occur due to primary infection or secondary to placental injury as a part of an immune response. Inflammation of the cord i.e. funisitis generally indicates a more advanced inflammatory

Table 2
Comparison of histopathological changes in the placentae of cases and controls.

Histopathological changes	Cases (n = 27) Number (%)	Controls (n = 27) Number (%)	p-value	Relative risk (95 % confidence interval)
Features of Maternal vascular malperfusion (MVM)				
Villous infarcts (VI)	12(44.4)	7(25.9)	0.158**	1.47(0.88–2.46)
Retroplacental hematoma (RPH)	11(40.7)	1(3.7)	0.001***	2.40(1.57–3.66)
Accelerated villous maturation (AVM)	13(48.1)	2(7.4)	0.001***	2.41(1.51–3.84)
Distal Villous Hypoplasia (DVH)	17(63.0)	4(14.8)	<0.0001***	2.67(1.52–4.67)
Acute atherosclerosis/ fibrinoid necrosis	7(25.9)	0(0.0)	0.010***	–
Persistent muscularization of basal plate arterioles (PMBPA)	2(7.4)	0(0.0)	0.491***	–
Basal Decidual Vessel thrombosis (BDVT)	3(11.1)	0(0.0)	0.236***	–
Mural hypertrophy of membrane arterioles (MHMA)	21(77.8)	3(11.1)	<0.0001***	4.36(2.10–9.09)
Ectatic vessel	9(33.3)	0(0.0)	0.002***	–
Persistence of intramural endovascular trophoblast (PIEVT)	5(18.5)	0(0.0)	0.051***	–
Features of Fetal Vascular Malperfusion (FVM)				
Chorioangiomas	13(48.1)	2(7.4)	0.001***	2.41(1.51–3.84)
Thrombosis of the fetal chorionic plate (TFCP)	5(18.5)	0(0.0)	0.051***	–
Avascular villi (AV)	3(11.1)	2(7.4)	1.000***	1.22(0.56–2.64)
Villous stromal-vascular karyorrhexis (VSVK)	2(7.4)	0(0.0)	0.491***	–
Intramural fibrin deposition	6(22.2)	0(0.0)	0.023***	–
Vascular ectasia (VE)	11(40.7)	2(7.4)	0.004***	2.16(1.38–3.38)
Additional findings				
Intravillous fibrin deposition (IVFD)	3(11.1)	0(0.0)	0.236***	–
Perivillous fibrin deposition	23(85.2)	6(22.2)	<0.0001***	4.95(1.98–12.34)
Maternal floor infarct (MFI)	3(11.1)	1(3.7)	0.610***	1.56(0.82–2.94)
Chorioamnionitis	8(29.6)	3(11.1)	0.091***	1.64(1.00–2.69)
Villous agglutination (VA)	2(7.4)	0(0.0)	0.491***	–

** : chi square test.

*** : Fisher's exact test.

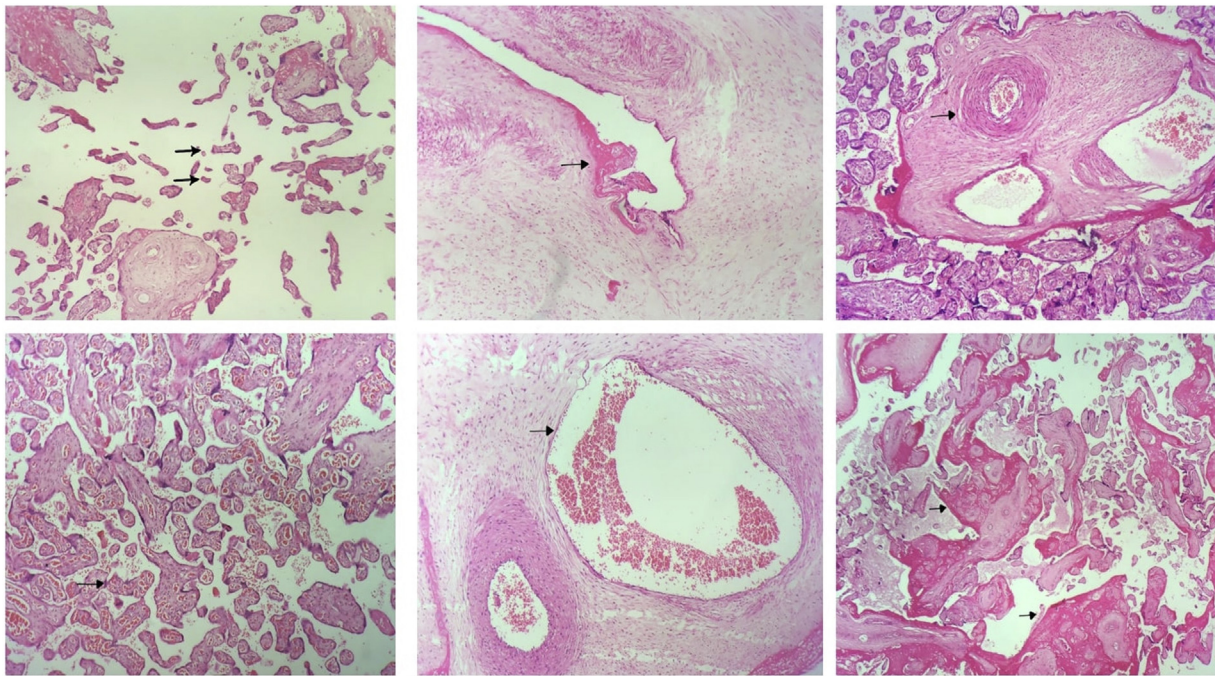


Fig. 1. Histopathological examination of placental sections (100x magnification; H&E stain) showing (from top left panel clockwise; black arrows): distal villous hyperplasia, fibrinoid necrosis, mural hypertrophy of membrane arteriole, perivillous fibrin deposition, vascular ectasia and chorioangiomas respectively.

process that involves the fetus [13]. In our study we found a significantly higher proportion of cases having perivillous fibrin deposition pointing towards a placental compromise.

SARS-CoV-2 infection can manifest as a systemic thrombotic and microvascular injury syndrome possibly due to complement activation. Similar findings have been reported by Mulvey et al. in the placental pathology of five full-term births of COVID-19 patients. Histology compatible with FVM i.e. focal avascular villi and thrombi in larger fetal vessels was found in all placentae. Vascular complement deposition in the placentas was not abnormal and staining for viral RNA and viral spike protein was negative. The outcomes of all the pregnancies were normal [14].

Rabiei et al. found evidence of clinical placental dysfunction in the form of absent umbilical artery end diastolic flow in two fetuses of a triplet pregnancy after SARS-CoV-2 infection of the mother. This led to a decline in the biophysical profile mandating an early lower segment caesarean section (LSCS) and premature delivery [15].

The presence of these findings may be due to the systemic effects of the virus rather than the virus per se. There are reports to prove the presence of the virus in the placental tissue. The virus in the placental tissue has been demonstrated by IHC, molecular and RTPCR based methods [16]. The detection of SARS-CoV-2 in the placenta of COVID-19 positive pregnancy with affection of multiple fetal cell types was seen by Facchetti et al., but they failed to demonstrate the presence of the virus in 14 other women who tested positive for COVID-19 and a number of changes of placental dysfunction were present in them. They concluded that the occurrence of mother-to-fetus SARS-CoV-2 transmission with adverse effects on the neonate is infrequent. The systemic nature of the disease is reflected in the placental changes of the SARS-CoV-2 positive pregnancies [17].

We observed that the placentae of the SARS-CoV-2 positive pregnancies projected the picture of pathological dysfunction, but the neonatal outcomes did not differ from SARS-CoV-2 negative pregnancies. Even in the presence of widespread placental

affliction, none of the neonates were positive for SARS-CoV-2 infection when tested within 48 h of life.

In a recent structured review by Sharps et al., 20 studies reporting placental histopathological changes in third trimester pregnancies were collated. FVM was reported in 35.3 % of cases, maternal vascular malperfusion in 46 % of cases and evidence of inflammation in 8.7 %. Only a minority of neonates tested positive. The authors concluded that due to the lack of a control group in these studies, limited conclusion could be drawn from these studies [18]. Our study too provides evidence that the transplacental transmission of SARS-CoV-2 infection to the fetus is a rare phenomenon.

In a systematic review of 108 pregnancies it was concluded that severe maternal morbidity and perinatal death with SARS-CoV-2 infection in pregnancy is possible. Maternal-fetal transmission of the SARS-CoV-2 virus was not detected in most of the reported cases in the review [19].

Even in the presence of placental injury, the neonatal outcomes have been consistently been good in COVID-19 pregnancies. In 242 pregnancies and their 248 newborns, risk of premature delivery was increased but none of the babies died and no vertical or horizontal transmission was documented [20].

Similarly Salvatore et al. found in their study that, of 116 mothers tested who positive for SARS-CoV-2 and 120 neonates who were delivered, all the neonates were tested at 24 h of life and none were positive for SARS-CoV-2. None of the neonates had symptoms of COVID-19 [21].

Findings similar to our study were also demonstrated by Baergen and Heller, who found evidence of fetal vascular malperfusion and thrombosis in 50 % of placentas out of 20 subjects [22]. Similarly Shanes et al. have shown increased prevalence of decidual arteriopathy and other features of maternal vascular malperfusion in COVID-19 placentas in comparison to controls, reflecting abnormalities in oxygenation within the intervillous space [5].

Our study highlights that placental injury is present even in asymptomatic or mildly symptomatic pregnant women positive

for SARS-CoV-2. Albeit evidence of placental injury neonatal outcomes were comparable amongst cases and controls. The cause for this is unknown and it is possible that this could be a characteristic of mild disease and as the severity of the disease increases the outcomes of the pregnancy could be affected. It could also suggest that despite the infection with SARS-CoV-2, sufficient time to cause significant dysfunction was not there given that most of these pregnancies were infected in the late third trimester.

Conclusion

Asymptomatic or mildly symptomatic SARS-CoV-2 positive pregnant women, with otherwise uncomplicated pregnancies, show evidence of placental injury at a microscopic level. The features of MVM, FVM and other features of placental inflammation are found more in the SARS-CoV-2 affected women when compared to controls. Similar findings have been reported by other investigators too. Although this dysfunction does not seem to result in poor fetal outcomes but may have adverse long term effects. This is an evidence that can't be ignored. A systemic nature of the disease and its ability to trigger a procoagulant state in the body may be responsible for the placental injury. The extent of this injury in symptomatic cases of SARS-CoV-2 positive pregnancies and its consequences on the outcomes need to be analysed.

CRedit authorship contribution statement

Nishtha Jaiswal: Conceptualization, Methodology, Data curation, Writing - original draft. **Manju Puri:** Conceptualization, Methodology, Supervision. **Kiran Agarwal:** Conceptualization, Methodology, Data curation, Investigation, Supervision. **Smita Singh:** Data curation, Investigation. **Reena Yadav:** Conceptualization, Methodology, Supervision. **Narendra Tiwary:** Software, Validation. **Purna Tayal:** Data curation. **Barkha Vats:** Data curation.

Declaration of Competing Interest

The authors report no declarations of interest.

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