

## A Study Depicting Histomorphology of Third Trimester Placenta in SARS-Cov-2 Positive Women

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### ABSTRACT

**Background:** This study aims to detect association of SARS-COV-2 infection in terms of histopathological changes in the third trimester placenta.

**Methods:** SARS COV 2 positive placenta cases received in Department of Pathology, Gandhi Medical College and Hamidia Hospital, Bhopal, Madhya Pradesh. 7 cases were sent for histopathological examination. Clinical details, history, details of relevant investigation like D-dimer, blood reports etc. was taken from the electronic medical records and requisition form received in the Department of Pathology. Histopathological findings were analyzed and recorded.

**Result:** This is a case series depicting various histopathological changes in term placenta of 7 SARS Corona Virus 2 (COV-2) positive women in the age group of 20 years to 35 years exhibiting symptoms ranging from mild to severe degree. The major histopathological finding noticed is under perfusion of placenta of maternal side in greater extent as compared to fetal side under perfusion followed by signs of inflammation of membranes viz chorionitis and chorioamnionitis. Hence, through the study, we want to highlight micro vasculopathy as one of the pathophysiological features of SARS Corona Virus 2 (COV-2) which might be leading to these histopathological findings and its correlation with elevated levels of D – Dimer.

**Conclusion:** Covid 19 positive women with third trimester of placenta do not express any specific histomorphological findings. Our study shows only signs of maternal and fetal vascular under perfusion with mild acute chorionitis which might have a relationship to a microvascular disease induced by SARS COVID 19 virus, yet this cannot be ruled out consistently proven several associated factors.

**Keywords:** SARS-Cov-2, Third Trimester, Placenta, Histomorphological Changes

### Introduction

With the recent pandemic of Coronavirus infection within a few months, hospitals can expect an influx of large numbers of Covid-19 positive cases. Coronavirus disease 2019 (COVID -19) is caused by SARS Corona virus 2, belongs to beta coronavirus family.<sup>1</sup> SARS-Cov-2 is an enveloped, single stranded RNA virus and it's composed of four structural proteins (Spike surface glycoprotein, envelop protein, membrane protein and nucleocapsid protein) and non –structural protein.<sup>2</sup> Studies showed that the spike protein of this virus binds to angiotensin converting enzyme 2 (ACE 2), which is a functional receptor for SARS Cov2<sup>3</sup>. The ACE expression receptor is high in lung, kidney, heart and ileum, so it primarily affects the respiratory system. The Placenta is the key organ at maternal / fetal interface and essentially function as the lungs and kidney for the fetus in utero.<sup>4</sup> Recent studies suggested that SARS Cov-2 can access the placental interface and potentially be transmitted to the foetus<sup>5</sup>. Studies have already analyzed the gross and histopathology of placenta in COVID -19 and would describe micro-vasculopathy and inflammatory response was rarely found.

We present a case series of six placentas of SARS-Cov2 positive women who had been diagnosed corona infection by RT-PCR before birth of baby. We provided a detailed histopathological finding of morphological changes in presence of SARS –CoV-2 infection in placental tissue.

### Materials and Methods

SARS COV 2 positive placenta cases received in the Department of Pathology at Gandhi Medical College, Bhopal and consisted of 7 cases have been sent for histopathological examination. To prevent infection, tissue was fixed for 48 hours then processed according to standard procedures. After fixation grossing was done with three sections of placental tissue as well as one section from the umbilical cord and chorionic membranes. These sections were processed into paraffin blocks and stained with Hematoxylin and Eosin stain. All mothers were tested positive via RT-PCR at Gandhi Medical College, Bhopal. Histopathological finding, according to Current Amsterdam Placental Workshop Group Consensus statement. Clinical information was taken from the electronic medical records, which given in Table 1.

**Result**

We enrolled 7 pregnant patients who were tested positive (both symptomatic and asymptomatic) for covid 19. All placenta were term deliveries (37<sup>th</sup> to 39<sup>th</sup> gestational weeks). The age of the patients ranged between 20 years to 35 years. 2 patients presented with mild symptoms (case 2, 4 & 7) fever, cough and dyspnea and other 4 cases were asymptomatic prior to delivery and in postpartum period also. All patients were delivered by caesarean section. Clinical and biochemical findings are summarized in table 1. Two patients (case 1 & 3) had a past history of hypothyroidism and oligohydramnios respectively. All infants were healthy & tested negative for COVID 19 by RT-PCR testing.

Histopathological findings are summarized in table 2. Diagnosis was made and graded using Current classification (Amsterdam system)

1. Maternal uterine / trophoblastic	3. Inflammation, infectious
Maldevelopment: Decidual arteriopathy Superficial implantation Malperfusion: Partial global: Accelerated villous maturation Complete segmental: Infarct, Infarction-hematoma Loss integrity: Abruptio placenta Marginal abruption, acute or chronic	Acute: Chorioamnionitis Villitis Intervillositis Chronic (TORCH) Villitis Intervillositis Deciduitis
2. Fetal stromal-vascular	4. Inflammatory, Idiopathic
Maldevelopment: Delayed villous maturation Villous capillary lesions Malperfusion: Partial global: umbilical cord compromise Complete segmental: fetal thrombosis Loss of integrity: Small vessel hemorrhage Large vessel hemorrhage Oedema Secondary / Extrinsic Meconium effects Increased nucleated red cells (NRBC)	Villitis/VUE Chronic deciduitis Fetal vasculitis, eosinophilic T cell Intervillositis, histiocytic 5. Pathogenesis incompletely understood Perivillous fibrin deposition, diffuse or localized 6. Other Malformation Tumors and heterotopias Morbidly adherent placenta Genetic / chromosomal abnormalities

**Findings of placenta with COVID 19**

Out of 7 cases fetomaternal vascular under perfusion was seen in 2 cases (28.5%) and maternal vascular under perfusion was seen in the rest of the 5 cases (71.4%). In

our study all placenta revealed term villi, there was no accelerated villous maturation seen. 3 Cases (2,4 & 6) (42.8%) showed increased syncytial knot formation. Signs of maternal vascular under-perfusion such as, infarction (not seen in our study), increased peri-villous fibrin deposition (seen in 4 cases) 57.1%, fibrinoid necrosis (seen in 5 cases) 71.4%, calcification (seen in 4 cases) 57.1%, retro-placental hemorrhage and inter-villous thrombosis (not seen in our study), were studied. Signs of fetal under-perfusion like thrombi in fetal circulation and chorangiomas were seen in case (1, 4) and case 4 respectively. Other signs such as fibrinoid necrosis, calcification, thrombi in fetal circulation, villous maturation, retroplacental hemorrhage, intervillous thrombosis, deciduitis & fetal vasculitis were absent in all other cases.

Signs of inflammation of placental membranes as chorionitis, chorioamnionitis were predominantly noted in 42.8% cases (2,3&5). One case (3), in which patient had cough, fever and oligohydramnios and fetal distress showed evidence of both acute chorionitis and chorioamnionitis possibly because of ascending infections.

**Discussion**

The effects of covid-19 in pregnant women and neonates are relatively unknown. Previous studies have studied the association of covid-19 with micro-vasculopathy, manifesting as maternal vascular under perfusion and fetal under perfusion.<sup>6</sup>

In our study we found both maternal and fetal under perfusion in only one case (14.2%) (case 1), although its effect on fetal and maternal health were insignificant, however 5 cases showed signs of maternal under perfusion. This suggests that effects of SARS covid-19 are prominent in mother and fetus are relatively unaffected due to maternal infection. Rebecca N Baergen and Debra S Heller [2020] have demonstrated furcated placenta in covid – 19 pregnant women, suggesting maternal covid 19 infections associated with a tendency of thrombi formation in fetal circulation. However, in our study no gross abnormality was found in terms of umbilical cord insertion (marginal insertion being normal)<sup>7</sup>. A study can be done in patients who were tested positive in first trimester in order to study in detail the mal insertion due to covid-19.

Asim Kichloo, Kirk Dettloff et. al Oct 2020 stated that COVID 19 has an association with hyper-coagulability because of elevation of D-dimer and it manifest as development of hypoxia induced ischemic changes and disseminated intravascular coagulopathy in one series. This goes in agreement with our findings of elevated D-DIMER values in 2 cases (28.5%).<sup>8</sup> In that case we found

**Tables: Clinical and biochemical findings in Covid 19 positive women (Table 1).**

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
<b>Age at birth, yrs</b>	30yr	23yr	25yr	28yr	33yr	43yr	26yr
<b>Gestational week</b>	38wks+5d	38wks	36wks+2d	37wk+4d	39wk+1d	39wks	38wks
<b>Types of birth</b>	CS	CS	CS	CS	CS	CS	CS
<b>Gravida/Para</b>	G1P0	G2P1L1	G1P1A0	G3P1A1L1	G1P0A0	G2P1A0	G1P0A0
<b>SARS CoV2 test positive prior to birth</b>	2days	1days	1days	3days	1 day	2 days	4 days
<b>Covid 19 related symptoms</b>	None	Mild cough, fever	Cough & fever	Mild cough, fever	None	None	Fever, cough
<b>Past medical history</b>	Hypothyroidism	None	None	None	None	None	None
<b>Pregnancy related complication</b>	Fetal distress	-	Oligohydramnios, fetal distress	None	None	None	None
<b>D-dimer (0-500 ng/ml)</b>	1.06	550	245	245	734	300	200

**Table 2: Histopathological findings.**

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Remarks
<b>Placental weight, g</b>	539	544	529	589	531	603	590	n.a.
<b>Term villi</b>	+	+	+	+	+	+		n.a.
<b>Syncytial knot</b>	-	+	-	-	+	++	+	n.a.
<b>Signs of maternal malperfusion</b>								
<b>1. Infarction</b>	-	-	-	-	-	-		
<b>2. Increased perivillous fibrin deposition</b>	+	+	++	-	-	+	-	0/7
<b>3. Fibrinoid necrosis</b>	+	+	+	-	+	+	+	4/7
<b>4. Calcification</b>	+	+	-	-	+	+	+	5/7
<b>5. Retroplacental hemorrhage</b>	-	-	-	-	-	-		4/7
<b>6. Intervillous thrombosis</b>	-	-	-	-	-	-		0/7
<b>Signs of fetal malperfusion</b>								
<b>1. Thrombi in the fetal circulation</b>	+	-	-	+	-	-	-	2/7
<b>2. Avascular villi</b>	-	-	-	-	-	-		0/7
<b>3. Karyorrhexis</b>	-	-	-	-	-	-		0/7
<b>4. Delayed villous maturation</b>	-	-	-	-	-	-	-	0/7
<b>5. Chorangiomas</b>	-	-	-	+	-	-	-	1/7
<b>Inflammatory changes</b>								
<b>Chorioamnionitis</b>	-	-	+	-	-	-		1/7
<b>Chronic villitis</b>	-	-	-	-	-	-	-	0/7
<b>Chronic deciduitis chorionitis</b>	-	-	-	-	-	-	-	0/7

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Remarks
Choriovasculitis	-	+	+	-	+	-	-	3/7
Fetal vasculitis	-	-	-	-	-	-		0/7
Placenta accrete	-	-	-	-	-	-		0/7
Marginal insertion of the umbilical cord	- +	- +	- +	- +	- +	- +	- -	0/7 n.a.
Hyper coiling of umbilical cord	-	-	-	-	-	-	-	n.a.
Phagocytosis of meconium	-	-	-	-	-	-	-	n.a.
Diffuse villous edema	-	-	-	-	-	-	-	n.a.
Umbilical cord (2 Artery and 1 vein)	+	+	+	+	+	+	+	No abnormality

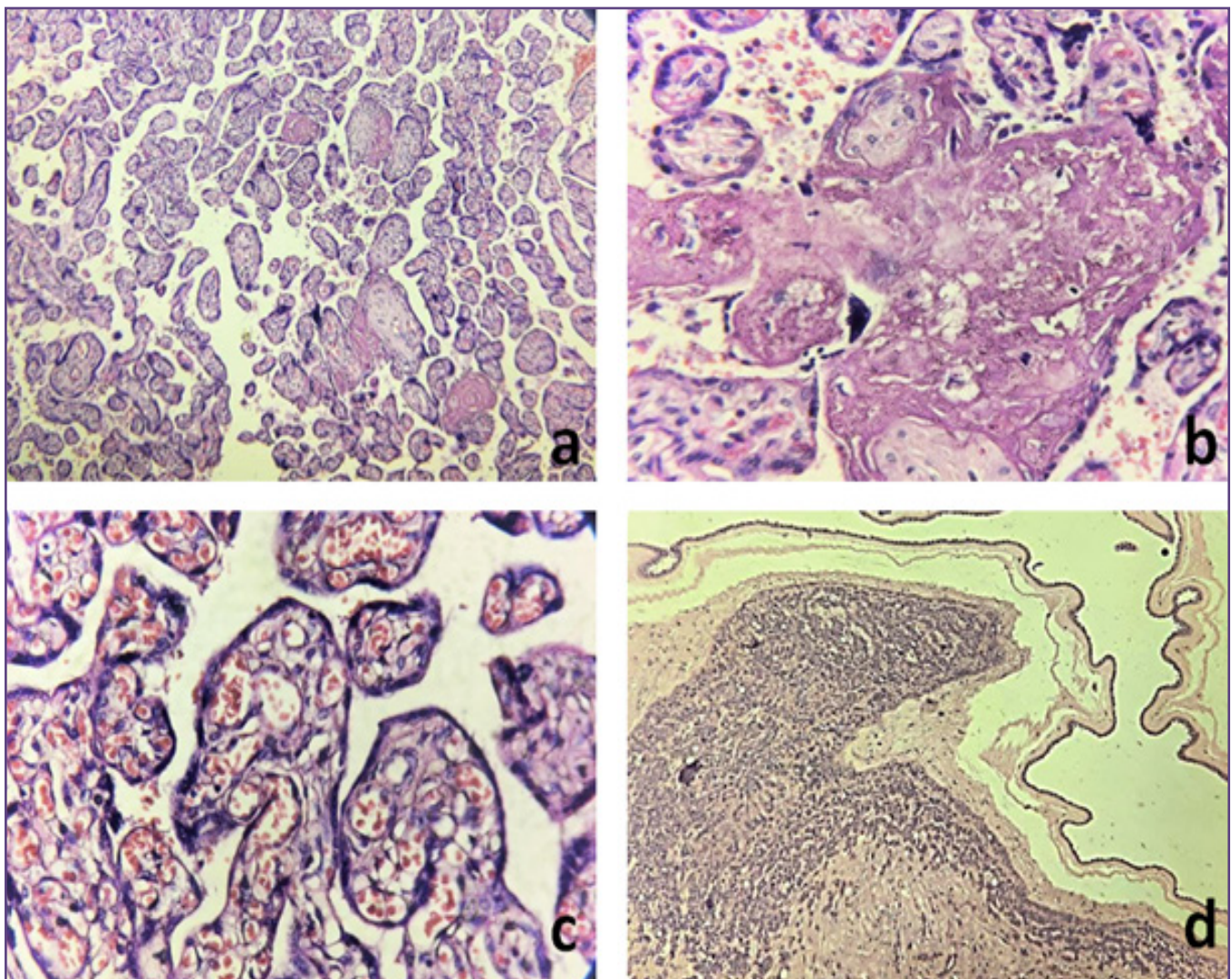


Fig. 1: Findings of placenta with COVID 19 a. Macroscopic image showing placental parenchyma b. Increased intervillous fibrin deposition as a sign of maternal malperfusion C. Chorangiomas, sign of fetal malperfusion (40x) d. Chorioamnionitis (40x).

increase perivillous fibrin deposition, fibrinoid necrosis and chorionitis.

Shanes et al. May 2020, investigated 16 COVID 19 positive cases showing signs of fetomaternal malperfusion. Among them only 2 cases (28.5%) showed chronic villitis. Signs of inflammation of placental membranes as chorionitis, chorioamnionitis were predominantly noted in 42.8% cases (2,3&5) in our study. One symptomatic patient with complicated pregnancy and signs of fetal distress showed evidence of both acute chorionitis and chorioamnionitis possibly because of ascending infections, not attributable to covid-19.

The confounding factors like hypertension, diabetes mellitus and obesity should be considered before attributing such changes for SARS covid -19. In our study we enrolled patients without any such comorbidities and we didn't find changes which were seen in other studies. Pregnancy anyways is a hypercoagulable state, so further studies are needed to attribute these findings to covid-19. At present we don't have sufficient evidence to comment on the impact of covid-19 on placenta and thus on fetal health.

## Conclusion

To conclude, Covid 19 positive women in third trimester of placenta do not express any specific histomorphological findings. Our study shows only signs of maternal and fetal vascular under perfusion with mild acute chorionitis which might have a relationship to a microvascular disease induced by Corona 2 virus, yet this cannot be ruled out consistently proven several associated factors. We do not rule out the impact of corona virus infection in early pregnancy.

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## Competing Interests

None

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