Histopathological Study of Placenta in COVID-19 Positive Mothers in a Tertiary Care Hospital, South Kerala

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ABSTRACT

BACKGROUND

The coronavirus disease 2019 (Covid-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is a global public health emergency. Data on the effect of coronavirus disease 2019 in pregnancy is limited to few case series. The purpose of this study was to describe the histopathological findings in the placentas of women with Covid-19 during pregnancy.

METHODS

Pregnant women with Covid-19 who delivered between August 1, 2020 and May 10, 2021, at Government Medical College, Trivandrum were considered for the study. Handling of specimens were carried out using Indian council of medical research (ICMR) guidelines for Covid-19 specimens. Placentas underwent routine clinical examination and processing. Clinical information was retrieved from the medical records. Histological examination was performed and features classified into maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM).

RESULTS

50 placentas from patients with severe acute respiratory syndrome coronavirus 2 were examined [33 patients delivered at term, 12 patients were preterm, 4 cases were intrauterine fetal demise and 1 case was medical termination of pregnancy (MTP)]. Patients with risk factors for maternal and fetal vascular malperfusion were excluded. 8 cases showed features of maternal vascular malperfusion and 11 cases showed features of fetal vascular malperfusion. Among intra uterine fetal death (IUFD) cases, 2 cases showed features of vascular malperfusion, 7 cases showed low grade acute inflammatory pathology which needs further studies with a greater number of cases to establish relationship with Covid-19 virus.

CONCLUSIONS

Covid-19 placentas showed increased rates of maternal and fetal vascular malperfusion. These changes may reflect a hypercoagulable state influencing placental pathology and hence an increased antenatal surveillance for women diagnosed with SARS–CoV-2 infection may be warranted. Further studies with control groups are necessary to determine the reproducibility and significance of these initial findings.

KEYWORDS

Covid-19, Pregnancy, Maternal Vascular Malperfusion, Fetal Vascular Malperfusion.

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BACKGROUND

The coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 named '2019 - nCoV' or '2019 novel coronavirus' or 'COVID-19' by the World Health Organization (WHO) is in charge of the current outbreak of pneumonia that began at the beginning of December 2019 near in Wuhan City, Hubei Province, China. SARS–CoV-2 is an enveloped, non-segmented, positive-sense RNA viruses belonging to the family Coronaviridae, order Nidovirales. Since its first identification, the disease has rapidly panned all across the world becoming a public health emergency of international concern by the World Health Organization (WHO). Severe acute respiratory syndrome coronavirus 2 belongs to the beta-coronavirus subgroup, and it has genome similarity of about 80 % and 50 % with SARS–CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) respectively. Coronaviruses mostly cause gastrointestinal and respiratory tract infections and are categorized into four major types: Gamma coronavirus, Delta coronavirus, Beta coronavirus and Alpha coronavirus. Six types of human CoVs have been formally recognized - HCoVHKU1, HCoV - OC43, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), HCoV229E and HCoV - NL63. Among these, SARS-CoV and MERS-CoV are known to be extremely pathogenic.[1,2]

The diagnosis of COVID-19 depends on clinical features and laboratory tests. Clinical manifestations include fever, dry cough and fatigue but presentation can be variable, ranging from asymptomatic to fatal pneumonitis. Patients vary from those with mild symptoms and those with co-morbid conditions like diabetes mellitus, coronary artery disease and malignancies. Patients with co-morbid conditions are at greater risk of developing complications. The gold standard for the diagnosis of SARS–CoV-2 infection is the identification of viral genetic material by RT-PCR, with greater sensitivity in bronchoalveolar lavage and nasopharyngeal swab. Regarding serology, a wide range of different tests is available, with variable sensitivity and specificity, most of which require validation. Laboratory tests such as complete blood count, C–reactive protein (CRP), D-dimer, clotting tests, lactic dehydrogenase (LDH), ferritin, and procalcitonin identify risk of disease with greater severity. Imaging tests may be useful for diagnosis, especially when there is a compatible clinical picture, and other above-mentioned tests are negative or unavailable.[3]

Analysing the history, the 1918 influenza pandemic caused a mortality rate of 37 % among pregnant women compared to 2.6 % in general population, the 2002 - 2003 severe acute respiratory syndrome (SARS) epidemic caused intensive care unit (ICU) admission for 50 % of pregnant women with 33 % requiring mechanical ventilation and the mortality rate was as high as 25 % for these women.[1] The impact of Covid-19 on pregnant women is of particular interest to obstetricians. There is a very limited data currently available on maternal outcomes in COVID-19 infection in pregnancy. Several adverse outcomes have been reported in pregnant women affected with Covid-19 which includes miscarriage, intrauterine fetal death, preeclampsia, preterm delivery, maternal critical illness & neonatal deaths with conflicting results regarding antepartum or peripartum vertical transmission.[4] Histopathological findings in placentas from pregnant women infected with viruses have been reported in the literature.[5,6] However reports on placental pathology in Covid-19 infected mothers is limited to a few case series.[7-10] Objective of this study was to assess the histopathological findings in placentas of pregnant women infected with Covid-19 and to find out whether these changes have significant clinical implications on the mother and foetus.

METHODS

It is a cross sectional study conducted from August 1, 2020 to May 10, 2021. The study was conducted in the Department of Pathology, Government Medical College, Trivandrum. Pregnant women with Covid-19 who delivered between above mentioned dates were considered for the study. Placentas were received from 50 Covid-19 positive women in the Department of Pathology at Government Medical College, Trivandrum. The study was registered with the institutional review board and was approved by ethics committee (No: 07/61/2020/MCT). Due to infectious nature of the tissue, fixation for 48 hours was allowed prior to dissection. Handling of specimens were carried out using ICMR guidelines for Covid-19 specimens. All placentas were examined for gross and histologic findings following the Amsterdam consensus statement guidelines.[11] Clinical information including age, parity, gestational age, mode of delivery/outcome, associated medical disorders of all patients were retrieved from the medical records. Testing for Covid-19 was not performed on placental tissue. All mothers and infants were tested via RT–PCR/RAT/True Nat at Government Medical College, Trivandrum.

Statistical Analysis

Data was recorded using Microsoft Excel. Patient characteristics were summarized using descriptive statistics. Categorical data were described using frequency and percentages.

RESULTS

Clinical Findings

Average maternal age was 28 years and predominantly multigravidae (27/50). All births were singletons. The caesarean delivery was 50 % mostly performed for fetal indications. Fifty placentas from patients with SARS–CoV-2 were examined. Thirty-three patients delivered at term (37-40 weeks). Twelve patients were preterm, four cases of intrauterine death and one case of medical termination of pregnancy. 46 out of 50 patients belong to the category B1 (asymptomatic cases) and 4 cases belong to category B2 (symptomatic cases/those with comorbidities).[12] There were no maternal or neonatal death in our series. All infants tested were negative for SARS–CoV-2 by RT-PCR.

Placental Gross and Histopathology

All placentas were examined for gross & histological findings following the Amsterdam guidelines. Grossly there were umbilical cord insertional anomalies (9 of 50 cases) & retroplacental clots (2 of 50 cases). Features of maternal vascular malperfusion (MVM) were present in 21 cases (42 %). Features included villous infarction (10 of 21 cases), Distal villous hypoplasia (9 of 21 cases), accelerated villous maturation (1 of 21 cases), decidual arteriopathy (5 of 21 cases) & retro placental hematoma (2 of 21 cases). [Figure 1, 2]

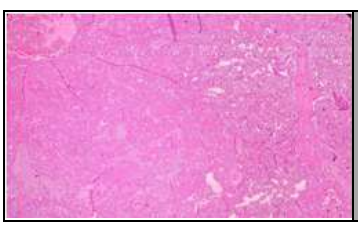

Figure 1. Infarction Showing Crowding of Villous Structure on Left Half and Viable Structures on Right Half

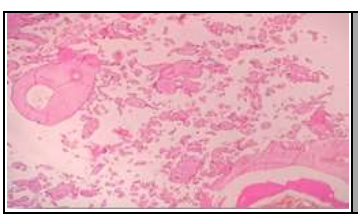

Figure 2. Distal Villous Hypoplasia with Thin and Elongated Villi

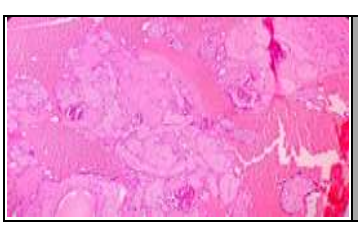

Figure 3. Focus of Avascular Villi Mixed with Areas of Haemorrhage

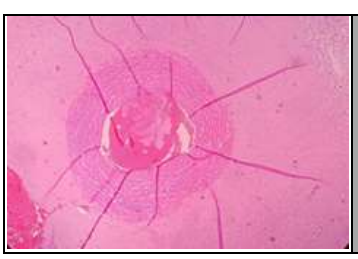

Figure 4. Thrombus Formation in Fetal Artery

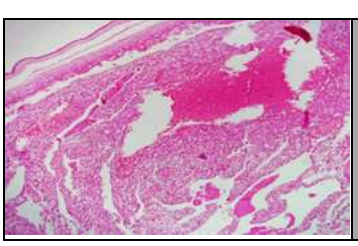

Figure 5. Acute Chorioamnionitis: Polymorphonuclear Leucocytes Extend to Fibrous Chorion and Amnion

Features of fetal vascular malperfusion (FVM) were present in 24 cases (48 %). Features include clustered avascular villi (2 of 24 cases), mural thrombi in fetal vessels (9 of 24 cases), stem vessel obliteration (4 of 24 cases) and vascular ectasia (14 of 24 cases). [Figure 3, 4]

7 Covid-19 cases showed acute inflammatory pathology corresponding to maternal (5 cases) & fetal inflammatory response (2 cases) (Grade 1 response). [Figure 5]

DISCUSSION

The typical course of SARS–CoV-2 infection and its clinical sequelae in humans is still being studied. The disease has an incubation period of up to 14 days, with a median time of 4 to 5 days from exposure to symptom onset. The disease illness severity varies from asymptomatic carriers to critical with involvement of vital organs such as the lungs, liver, the gastrointestinal tract, heart, the central nervous system, kidneys and the blood. Multisystem involvement is associated with increased mortality and poor outcome. The main mechanism described is the high binding affinity of the SARS–CoV-2 virus with the angiotensin converting enzyme (ACE2) receptors that are widely expressed in most human cells. Multisystemic nature of the disease may be related to the tropism of the virus for the ACE-2 receptors located on several different human cells. The highest levels of SARS–CoV-2 copies were detected in the respiratory tract, while the levels detected in other organs like kidneys, liver, heart, brain and blood were lower. These findings indicate a possible organ tropism of SARS–CoV-2 that might influence the course and outcome of the disease. The exact pathogenesis of receptor functioning, whether treatment with angiotensin receptor blockers and ACE inhibitors modifies this expression and whether patients with comorbidities have higher expression of ACE2 receptors are still being studied.[13] Another point of interest to mention is that Covid-19 infections are associated with prothrombotic state with development of ischemic changes of fingers and toes and in some patients, with features of disseminated intravascular coagulopathy. The main mechanism described is that Covid-19 can activate coagulation cascade through various mechanisms, leading to severe hypercoagulability and abnormality in D–dimer-based coagulation factors. Thus, early anticoagulation may block clot formation and reduce microthrombus, thereby reducing the risk of major organ damages.[14] This is a brief report of initial findings seen in placentas of Covid-19 positive mothers.

Maternal vascular malperfusion represents a recognizable pattern of placental injury related to altered uterine and intervillous blood flow. MVM consists of a constellation of placental pathologic findings seen in the maternal decidual vessels and villous parenchyma, reflecting abnormal spiral artery remodelling, abnormalities in oxygenation and flow dynamics in the intervillous space.[15] Maternal vascular malperfusion has been associated with oligohydramnios, fetal growth retardation, preterm birth & still birth. Risk factors include maternal hypertensive disorders (major risk factor),[7] hypercoagulable states, lupus anticoagulant and diabetes mellitus (overt & gestational diabetes mellitus).[16] A study conducted over 16000 placenta examined the prevalence of decidual vascular lesions of MVM, classic one being acute atherosis, and found its presence in 0.4 % of uncomplicated pregnancies, but at higher frequencies in patients with preeclampsia (10.2 %), fetal death (9 %), small for gestational age neonates (1.7 %), spontaneous preterm labor and premature rupture of membranes (1.2 %). The diagnosis of MVM is based on a constellation of findings involving primary changes in the maternal decidual vasculature and/or secondary villous

parenchymal changes rather than single finding either seen grossly or under microscope. Gross findings of MVM include placental hypoplasia, placental infarction, and retroplacental haemorrhage. The histologic lesions seen in MVM involves both the maternal decidual vasculature and the chorionic villi. The Amsterdam placental workshop group consensus statement defines villous maldevelopment, specifically distal villous hypoplasia and accelerated villous maturation as the most important histologic finding of MVM, but also recommends that the finding of decidual arteriopathy be noted in the pathology report.[17] In our study, out of 21 cases of MVM, 6 were having hypertensive disorders, 2 were having hypercoagulable states and 5 were having diabetes mellitus (1 case of overt diabetes mellitus & 4 case of gestational diabetes mellitus). Excluding the cases with risk factors, in the rest 8 cases major histological findings were distal villous hypoplasia (4 of 8 cases) followed by villous infarction (2 of 8 cases), decidual arteriopathy (1 of 8 cases) and accelerated villous maturation (1 of 8 cases).

Fetal vascular malperfusion is the recommended new terminology for fetal thrombotic vasculopathy by the Amsterdam placental workshop consensus statement. Site of involvement can be anywhere in the vascular tree starting from umbilical vessels through chorionic vessels and stem villi ending with the terminal villi. Multiple placental, maternal, and fetal underlying aetiologies can result in FVM and includes abnormal insertion, length & coiling of umbilical cord, maternal vascular malperfusion, fetal cardiac dysfunction/malformations, polycythaemia, large vascular anomalies and severe fetal inflammatory response to ascending intrauterine infections. Fetal vascular malperfusion has been strongly associated with adverse perinatal outcomes which includes fetal growth restriction, thromboembolic events leading to necrosis of multiple fetal organs including liver, renal vessels, lungs and myocardium, intrauterine fetal demise and increased obstetric and maternal complications. Major histological findings include stem villous obliteration (fibromuscular sclerosis), intramural fibrin deposition, avascular villi, thrombosis of fetal chorionic plate or umbilical vessels and villous stromal-vascular karyorrhexis (haemorrhagic endovasculitis).[18] In our study, out of 24 cases of fetal vascular malperfusion, 7 cases were having maternal vascular malperfusion, 5 cases were having marginal insertion of umbilical cord and 1 case was having cardiac anomaly. Excluding the risk factors, in the rest 11 cases, major histological findings were mural thrombi in fetal vessels (4 of 11 cases), vascular ectasia (3 of 11 cases) clustered avascular villi (2 of 11 cases) and stem vessel obliteration (2 of 11 cases).

There were 4 cases of intrauterine fetal death (IUFD) and 1 case of MTP. Indication for MTP was fetal anomalies. Histopathology showed stage1 maternal inflammatory response only. Among intrauterine fetal death (IUFD) cases, cases 1 & 2 showed features of maternal & fetal vascular malperfusion (Category B1, no risk factors). Case 3 showed features of abruption and fetal vessel mural thrombi (Category B2, no risk factors). Case 4 showed features of clustered avascular villi, stem vessel obliteration and fetal inflammatory response stage 1 (Category B1, high risk based on anomaly scan). 7 Covid-19 cases showed acute inflammatory pathology. In all cases inflammatory response was low grade. Low stage inflammation is common in laboring deliveries & bacterial investigation are frequently negative.[19] Further studies with more number of cases are needed to define the relationship between Covid-19 virus and acute inflammation.

CONCLUSIONS

We report placental pathology from 50 patients with SARS–CoV-2 infection. There were increased rates of maternal & fetal vascular malperfusion suggesting a common theme of vascular pathology. These findings suggest that an increased antenatal surveillance for women diagnosed with SARS–CoV-2 infection may be warranted. Further studies with control groups are necessary to determine the reproducibility & significance of these initial findings.

Limitations of This Study

This study has some limitations. Firstly, we did not use distinct control groups. Only placentas associated with Covid-19 infections were included for the study. Also, we did not categorize the risk factors associated with maternal and fetal vascular malperfusion based on severity. Therefore, whether the low grade or the high-grade factors resulted in placental pathologies could not be properly explained & hence therefore some findings may be unrelated. Finally, we did not describe a general threshold for the histological findings for the diagnosis of MVM and FVM. As Covid-19 is a novel disease, our motive of the study is to find out any change in placenta as an initial study in our institution.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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