International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Prospective Hospital Based Study of Placental Changes to Identify Antenatal and Perinatal Transmission of Sars CoV2 Infection

This research article is a funded study, under the
Dr. M.G.R Educational and Research Institute, (Deemed to be University), Chennai, Tamil Nadu, India

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Abstract: ***Aim: To study the placental changes in mothers exposed to Covid 19 and to identify antenatal and perinatal transmission of SARS CoV2 infection. Method: This is a prospective observational study conducted over 18 months in all pregnant women with history of Covid symptoms and RT-PCR positive for Covid-19 or and SARS CoV Antibodies positive any time during the course of pregnancy or at the time of delivery. Results: A total of 60 cases, 30 Covid positive and 30 Covid negative mothers were included in the study. There was no statistical significance among the gravida or mode of delivery. Preterm deliveries were more in number in Covid positive mothers. Clinical presentation of covid symptoms and history of exposure to cases of covid positive patients was statistically significant (p<0.001 to p=0.0080). Histopathological study of covid positive placenta revealed increased incidence of chorioamnionitis, MVP, decidual arteriopathy, chorangiosis, calcification and hyalinization (p=0.0001 to 0.0003). Sars CoV2 and ACE 2 expression was not statistically significant among the two groups (p=0.5). Conclusion: There is increased incidence of placental changes such as MVP, decidual arteriopathy, increased syncytial knots, calcification in covid infected mothers and thereby affecting the new born. However, the exact association between these changes and ACE 2 & Sars CoV2 expression could not be established, also whether these are true markers for placental infection needs further study.***

Keywords: COVID-19, Chorioamnionitis, pregnancy, Immunohistochemistry

1. Introduction

The 2019 coronavirus disease (COVID-19), a novel zoonotic disease was first discovered in late December 2019 following an outbreak of severe pneumonia of unknown etiology in Wuhan, Hubei Province, China (1). The virus, with an incubation period of 5 days (range, 2–14 days), results in symptoms including headaches, fever, diarrhoea, myalgia, cough, severe respiratory illness and death depending on its severity (2). Some studies suggest, perinatal risks and pregnancy outcomes appear to be related to the severity of the illness in women with COVID-19(3). There is an ongoing effort to understand transmission, incidence, disease pathogenesis and the short- and long-term impacts following infection. In particular, the impact of SARS-CoV-2 infection on mothers and their babies. Evidence suggests that pregnant women with COVID-19 are more susceptible to severe disease with a higher risk of preterm birth, as well as higher risk of maternal and/or fetal death (4). The establishment of vertical transmission of COVID-19 is limited to date (5). The main binding receptor for SARS-CoV-2 on host cell is angiotensin-converting enzyme 2 (ACE2) receptor. SARS-COV-2 is thought to enter the placenta by the spike protein binding to angiotensin-converting enzyme 2 (ACE2). Levels of ACE2 are theorized to decline throughout pregnancy (6). While lung cells are the primary targets of this respiratory virus, causing acute respiratory distress syndrome. SARS-CoV-2 also affects other ACE2-expressing tissues including those of the cardiovascular system (8). The placenta offers a protective barrier that does not allow the fetus to become exposed to maternal infections. The human placenta primarily consists of a number of specific fetal-derived cells called trophoblasts, of which there are three main types. These include terminally differentiated multinuclear syncytiotrophoblast cells, which are in direct contact with the maternal blood and line the villus tree, progenitor villous cytotrophoblast cells, which underlie the syncytiotrophoblast, and invasive extravillous trophoblast (EVT) cells, which anchor the chorionic villi to the uterus and modify its vasculature (4). However, frequent abnormal findings in placental pathology have been reported among COVID-19-positive mothers (5). ACE2 is expressed in the placenta and is found in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle from both primary and secondary villi. Innovative methodical research found evidence that ACE2 is expressed in various gynecologic organs such as the ovary, uterus, and vagina. Overall, ACE2 expression has been seen in numerous tissues in direct relation with developing pregnancies that could be associated with adverse maternal-fetal outcomes (7). Histopathologic examination of placental tissue can contribute significant information regarding the health of both mother and fetus. A variety of viral infections in pregnancy are associated with specific placental findings, including lymphoplasmacytic villitis with associated enlargement of villi and intravillous hemosiderin deposition in the setting of maternal cytomegalovirus infection (8). ACE2 is expressed in the placenta and is found in the syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle from both primary and secondary villi (9).

Aims and Objectives

a) To correlate the histopathological findings of placenta among Covid Positive mothers in comparison with Covid negative mothers.
b) To correlate the immunohistochemistry of SARS-COV-2 and ACE 2 expression in placentas among Covid Positive in comparison with Covid negative mothers.
c) To assess the neonatal outcome and compare in both the scenarios.

2. Materials and Method

This is a hospital based prospective observational study conducted in a tertiary care hospital Rajarajeswari Medical college and hospital, Mysore Road, Bangalore, after seeking permission from the institutional ethics committee during the 2nd wave of Covid period beginning from Oct 2021 to March 2023. The study population comprised of pregnant women with history of Covid symptoms and RT-PCR positive for Covid-19 or and SARS CoV Antibodies positive any time during the course of pregnancy or at the time of delivery. Pregnant women who were RTPCR negative, Antibodies negative or those who had no symptoms of Covid throughout their entire course of pregnancy were considered as control samples.

According to the hospital protocol, all pregnant ladies were mandatorily tested for Covid during their pregnancy and admitted to the hospital for delivery. Demographic details of both the cases and the control samples which included their personal data, obstertric history, history of Covid symptoms, gestational diabetes, pre-ecclampsia etc were recorded. The mode of delivery of the baby, its birth weight, APGAR scores, neonatal well-being etc were also noted.

The placentas were collected after obtaining informed consent from all patients and transported in 10% formalin to the pathology department. Gross examination of the placenta was carried out and weighed and after through fixation they were taken for processing. The umbilical cord and placental membranes was made a note and a minimum of 3 bits each from the maternal side and the foetal side of placenta were obtained for HPE processing. The H & E stained slides were studied and analysed under the microscope to study the histopathological changes of Covid placentas and compared with that of control placentas.

Later, one block per case was selected by the pathologist and Immunohistochemistry for 2 markers, ACE2 & SARS-CoV obtained from BIO SB, Sentier labs, Hyderabad were tested on Formalin –Fixed Paraffin Embedded (FFPE) tissues. Antigen retrieval was done by heat induced epitope retrieval method. Membranous and cytoplasmic expression for ACE 2 and only membranous expression for SARS CoV 2 were analysed. Appropriate positive and negative control samples were run with each batch of the samples tested. For ACE 2-renal tissue from autopsy case were taken as control. For SARS CoV2 – lung tissue from a proven case of COVID was taken as positive control.

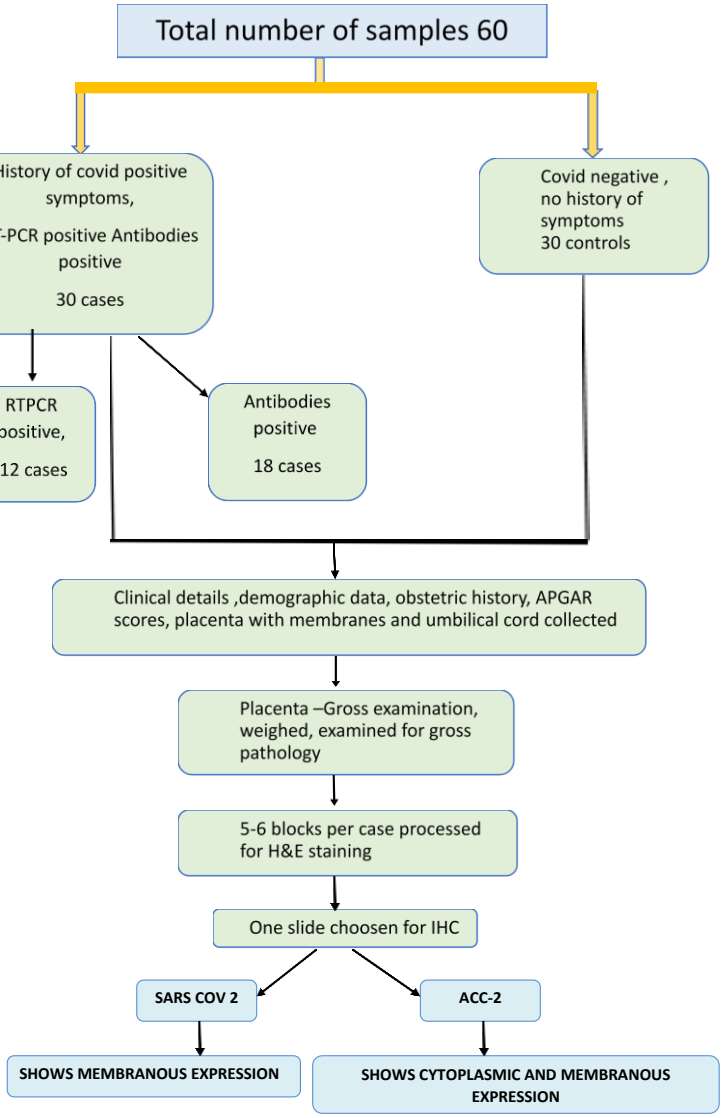
3. Results

Descriptive statistics

A total of 60 cases, 30 Covid positive and 30 Covid negative cases were included in the study. Out of the 30 Covid positive cases, 12 cases were positive by RTPCR and remaining 18 of them showed positivity for SARS- COVCovid antibodies. All these patients presented with mild symptoms of fever with or without cough either during their course of pregnancy or delivery. The control cases had no symptoms of Covid anytime during their entire pregnancy and delivery and tested negative.

The age ranged from 19-32 years with many of them being first time mothers. The incidence of Gestational diabetes among the covid and non-covid mothers was not significantly different but pre-ecclampsia was almost 3-fold increased in Covid infected mothers.

On HPE examination, there were increased incidence of changes of Maternal vascular perfusion, Fetal vascular Perfusion, Chorangiosis of placenta along with evidence of Chorio-amnionitis of the placental membranes in Covid infected mothers when compared to Control samples.



Neonatal outcome:
In the control samples (33), only 40 % (n=12) were IUGR babies while 60 % (n=18) cases were term babies. Whereas in Covid infected mothers (27), almost 60 % (n=18) were IUGR and only 26 % (n=8) were delivered at term.

Table 1: Demographic details of study subjects

Variable	COVID Positive (n=27)	COVID Negative (n=33)	P-Value
Age Group			
<20	1 (3.70%)	1 (3.03%)	0.9095
20-30	25 (92.59%)	30 (90.91%)	
>30	1 (3.70%)	2 (6.06%)	
Mode of delivery			
Vaginal	16 (59.26%)	16 (48.48%)	0.4053
LSCS	11 (40.74%)	17 (51.52%)	
Obstetric history			
Primi gravid	12 (44.44%)	17 (51.52%)	0.5856
Multiple Gravid	15 (55.56%)	16 (48.48%)	
Pre-term	15 (55.56%)	12 (36.36%)	0.1371
Full term	12 (44.44%)	21 (63.64%)	

Inference: It is evident that most of the mothers in both cases and control group were between 20 to 30 years of age. There was no statistical significance in the mode of delivery whether Vaginal or LSCS among the groups. Most of the covid positive mothers were multigravida compared to covid negative mothers who were primigravida, although this has no statistical significance. In comparison to covid positivity among patients, full term births were more in number in covid negative mothers whereas preterm deliveries were seen in increased numbers in covid positive pregnancies.

Tables 2: Fetal outcome

Variable	COVID Positive (n=27)	COVID Negative (n=33)	P-Value
Birth weight			
>2.5 kg	13 (48.15%)	20 (60.61%)	0.345
2 to 2.5 kg	8 (29.63%)	10 (30.30%)	
<2 kg	6 (22.22%)	3 (9.09%)	
APGAR Score			
At 1 Minute	7.43±1.41	7.85±0.89	0.1655
At 5 Minutes	8.96±0.64	9.15±0.66	0.2654
Placental weight	358.15±126.19	359.71±63.36	0.9506
Umbilical Cord			
Normal	16 (59.26%)	27 (81.82%)	0.1474
Trueknot	2 (7.41%)	0 (0.00%)	
False Knot	6 (22.22%)	5 (15.15%)	
Short	3 (11.11%)	1 (3.03%)	

Inference: There was no statistical difference on the fetal outcome and birth weight of the newborns in our study population among covid positive and covid negative mothers. Also, the APGAR scores at 1 minute and 5 minutes showed

not much significance. On the contrary, the APGAR score at 24 hours after birth were significantly better in covid negative deliveries (93.94%) in comparison to covid positive deliveries with scores being >8 in 62.96%, 5 -7 in 22.22% cases and <5 in 14.8% of cases thereby exhibiting statistically significance of p=0.008. There was no much differences in the gross and microscopic changes in umbilical cord and placental membrane among the groups.

Tables 4: Placental changes

Variable	COVID Positive (n=27)	COVID Negative (n=33)	P-Value
Fibrinois Necrosis	20 (74.07%)	20 (60.61%)	0.2131
	7 (25.93%)	13 (39.39%)	
Calcifications	22 (81.48%)	12 (36.36%)	0.0007 (S)
	5 (18.52%)	21 (63.64%)	
Chorio-amnionitis	3 (11.11%)	3 (9.09%)	0.7657
	24 (88.89%)	30 (90.91%)	
Hyalinization	19 (70.37%)	17 (51.51%)	0.1663
	8 (29.63%)	16 (48.49%)	
Increased Synechial Knots	19 (70.37%)	7 (21.21%)	0.0003 (S)
	8 (29.63%)	26 (78.79%)	
Chorangiogenesis	3 (11.11%)	1 (3.03%)	0.2004
	24 (88.89%)	32 (96.97%)	
Terminal Mature Villi	5 (18.52%)	33 (100%)	0.0001 (S)
	22 (81.48%)	0 (0.00%)	
Decidual Arteriopathy	19 (70.37%)	3 (9.09%)	0.0001 (S)
	8 (29.63%)	30 (90.91%)	
Placental Weight	13 (48.15%)	23 (69.70%)	0.1240
	14 (51.85%)	10 (30.30%)	
Placental Infarcts			
Few	17 (62.96%)	1 (3.03%)	0.0001 (S)
Large	9 (33.33%)	2 (6.06%)	
Occasional	1 (3.70%)	10 (30.30%)	
Nil	0 (0.00%)	20 (60.61%)	

Inference: The microscopic study of placenta revealed increased foci of calcifications (81.48%), increased syncytial knots in the chorionic villi (70.7%), decrease in the number of terminal mature villi (81.48%) in covid positive pregnancies. Vascular malformations in placenta presenting as decidual arteriopathy were statistically higher (70.3%) in covid positive pregnancies in comparison to only 3 cases (9.09%) in covid negative pregnancies. These parameters were statistically significant with a p value of 0.0001 to 0.0007. The study of placenta revealed statistically significant results with increased incidences of placental infarcts (62.96%) in covid positive pregnancies vs covid negative pregnancies (3.03%). Normal growth and maturation were more in 20/33 (60.6%) cases of covid negative pregnancies compared to 0 cases in covid positive pregnancies.

Tables 5: SARS CoV and ACE 2

	COVID Positive (cytoplasmic and membranous expression) (n=27)	COVID Negative (n=33)	P-Value
ACE 2	27	33	0.5

Inference: In our study, ACE 2 expression (membranous and cytoplasmic positivity) was seen in a total 27 cases and negative in remaining 33 cases. There was no statistical difference among expression of ACE 2. On contrast, SARS CoV2 expression was not seen in any of the cases.

4. Discussion

Covid 19 infection has taken its toll in the second wave in the year 2021 by 57%. There is increase in the number of positive cases compared to first wave, affecting large number population, including pregnant women

Covid 19 can potentially affect the placenta in two ways. First, effects on maternal perfusion of the placenta can manifest as accelerated villous maturation, infarction, intervillous thrombi, extravillous trophoblastic lesions, and sbchorionic laminar necrosis in the membranes. Second, if the fetal circulation is affected, thrombosis of larger vessels, fibrous obliteration of vessels in the villi (villous sclerosis) and breakdown of the endothelial cells within the villous stroma (villous stromal vascular karyorrhexis) may be seen. (11)

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 malperfusions (MVM), as defined in the Amsterdam consensus. It is already known that MVM is a common finding in pregnancies complicated by preeclampsia and FGR. 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 <8mm at term.

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. 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 Acute or chronic inflammatory changes in these placentas were rarely found. However, microvascular changes and maternal vascular malperfusions (MVM) were almost a constant finding FVM is a term applied to a group of placental lesions indicating reduced or absent perfusion of the villous parenchyma by the fetus

FVM is an important risk factor for adverse pregnancy outcomes including FGR, fetal CNS injury, and stillbirth. FVM is diagnosed by the presence of vascular lesions in the fetal vessels in the placenta and the resultant changes in the downstream villi Even though the placental inflammatory response to SARS-CoV-2 is usually expected, most of the studies could not prove this on histopathological examination. Vertical transmission of SARS-CoV-2 from infected pregnant mother has always been a point of discussion since the beginning of COVID-19 pandemic. (13)

On histological examination, the placenta was remarkable for the presence of diffuse perivillous fibrin and an inflammatory infiltrate composed of macrophages as well as T lymphocytes, as demonstrated by IHC for CD68 and CD3. SARS–CoV-2 localized predominantly to the syncytiotrophoblast cells of the placenta, as demonstrated by IHC for the SARS–CoV-2 spike protein. The distinction between preeclampsia and COVID-19 is important, as it may have implications for the patient's future pregnancy outcomes.

SARS–CoV-2 localized to placental syncytiotrophoblast cells, the outer layer of multinucleated cells that cover the chorionic villi and that are in contact with maternal blood in the intravillous space. Syncytiotrophoblasts form a cellular layer between maternal and fetal circulation, contribute to transplacental transfer of protective antibodies, and, in some cases, are permissive to viral infection and to subsequent transmission to fetal cells.

The physiological adaptations and dynamics of the maternal immune system during pregnancy ensure the maintenance of defence mechanisms for maternal and foetal survival. Successful initiation of pregnancy is characterized by a pro-inflammatory and antiviral profile, followed by the anti-inflammatory or T helper 2 (Th2) stage allowing foetal growth, and a switch back to T helper 1 (Th1) or pro-inflammatory state at the third trimester. (3)

Cardiovascular diseases are linked to the development of severe and possibly fatal conditions of COVID-19. Thus, the pathology of COVID-19 does not seem to be explained merely by the action of SARS-CoV-2 entering host cells for destruction. Previous studies of the lung vasculature have proposed that SARS-CoV-2 spike protein-mediated cell signalling promotes the hyperplasia and/or hypertrophy of vascular smooth muscle and endothelial cells placental vascular remodelling occurred in all the pregnant women who become positive for SARS-CoV-2, even though they did not develop severe COVID-19, the spike protein may play a role in the mechanism.

The immune system changes during pregnancy in such a way that it adapts to the growth of a semi-allogenic fetus in the body of the mother, resulting in a distinct immune response to different infections during pregnancy. NK cells were also found to be functionally exhausted during SARSCoV-2 infection. Moreover, a reduction in circulating NK cell population has been reported during gestation. (4)

Various potential causes may play a role in the vertical transmission of the virus from the mother to the fetus. These include direct damage to the villous tree with a break in the protective syncytiotrophoblast layer, which could be caused by virus-induced apoptosis and vascular damage in the placenta, spread through the virus-infected maternal endothelium to the extravillous trophoblast, trafficking of infected maternal immune cells throughout the syncytiotrophoblast, paracellular or transcellular transport (for example, immunoglobulin-mediated transcytosis) into fetal capillaries, transmission via swallowed or aspirated amniotic fluid , as well as ascending infection from the vagina(4).

Relative to controls, COVID-19 placentas show increased prevalence of decidual arteriopathy and other features of MVM, a pattern of placental injury reflecting abnormalities in oxygenation within the intervillous space associated with adverse perinatal outcomes. Histopathologic examination of placental tissue can contribute significant information regarding the health of both mother and fetus.

COVID-19 patients showed a significant increase in intervillous thrombi. Intervillous thrombi are generally considered incidental findings The increased incidence of chorangiosis is notable as well. Chorangiosis is associated with decreased maternal oxygen saturation37,38; it is more commonly seen in women living at high altitudes,39 as well as for unknown reasons, in women with diabetes (10)

Immunohistochemistry staining was performed with specific monoclonal antibodies to detect SARS-CoV-2 antigen or to identify trophoblasts.

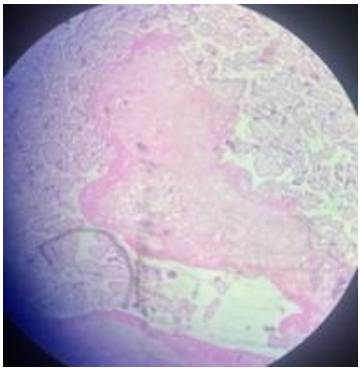
On histology, placental membranes showed decidua with scattered arterioles with thickened smooth muscle, consistent with hypertrophic arteriolopathy

Baud et al. described a second-trimester miscarriage in which the mother (nasopharyngeal swab) and placental submembranes and placental cotyledons were positive for SARS-CoV-2 on RT-PCR. Hosier et al. described SARS-CoV-2 localization to syncytiotrophoblast cells at the maternal-fetal interface of the placenta, with no evidence of vasculopathy. Chen et al described nine patients who had a caesarean section, with amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients all testing negative for SARS-CoV-2.

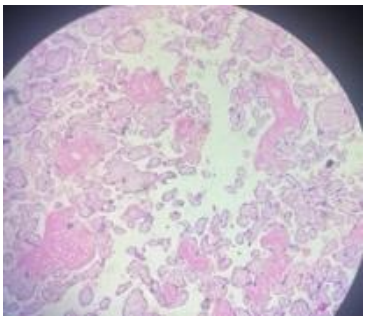
Placental vascular remodelling was found to occur in all of SARS-CoV-2-positive mothers as defined by RT-PCR. The major finding of this study is that the placental arteries of women who gave birth to live full-term newborns, but contracted SARS-CoV-2 during pregnancy, exhibited severe vascular remodelling. despite the occurrence of severe placental vascular remodelling, COVID-19 did not significantly impact the health of the newborn children according to the evaluations of appearance, pulse, grimace, activity, and respiration, as quantified by Apgar scores.

The present study found that placental vascular walls thickened and the lumen narrowed in women who gave live birth but contracted COVID-19 during pregnancy. Smooth muscle proliferation and collagen fiber deposition appear to play major roles in the development of placental vascular remodelling. (12)

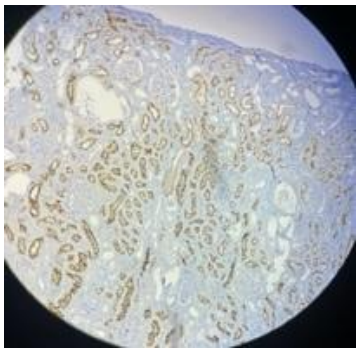
In this case, we did not find definitive evidence for fetal infection. However, future studies should further characterize SARS–CoV2 presence in the placenta and fetus through cellular colocalization studies and antibody-based electron microscopy analysis (14).



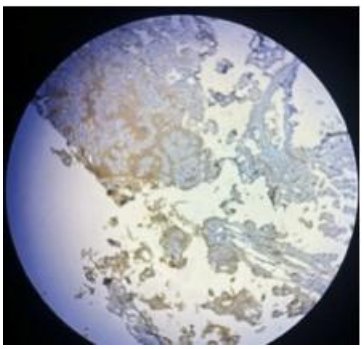
Photomicrograph of Covid positive Placenta –Maternal side showing hyalinization, H & E, 10X



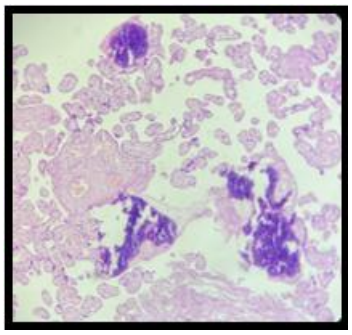
Photomicrograph of Covid positive Placenta showing fibrinoid necrosis of villi H & E, 10X



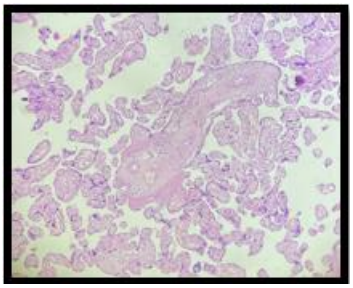
Photomicrograph of IHC -ACE 2 Control- Kidney Tissue



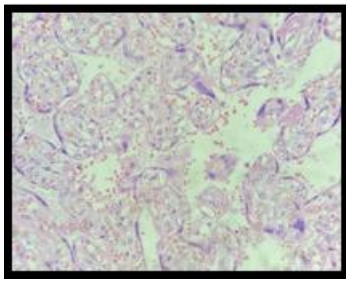
Photomicrograph of IHC ACE 2 – COVID Placenta (Term)



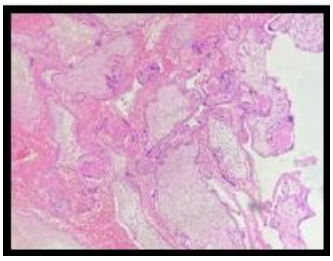
Photomicrograph of Placenta displaying Calcifications, H&E, 10X



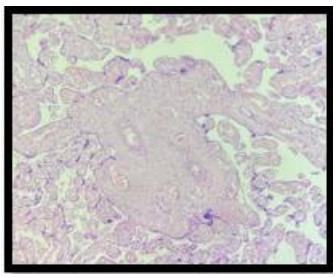
Photomicrograph of Placenta displaying increased syncytial knots &foci of fibrinoid necrosis, H&E, 10X



Photomicrograph of Placenta exhibiting Chorangiosis, H&E, 10X



Photomicrograph of Placenta showing Intervillous hemorrhage, H&E, 10X



Photomicrograph of Placenta showing thickened arteries, H&E, 10X

5. Conclusion

There is increased incidence of placental changes such as MVP, decidual arteriopathy, increased syncytial knots, calcification in covid infected mothers and thereby affecting the new born. However, the exact association between these changes and ACE 2 & Sars CoV2 expression could not be established, also whether these are true markers for placental infection needs further study.

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