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REVIEW ARTICLE: HISTOPATHOLOGICAL CHANGES IN PLACENTA AND RELATIONSHIP WITH CORONAVIRUS INFECTION DURING PREGNANCY

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Abstract

During Covid-19 pandemic, Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2) was significantly more severe in pregnant women than in non-pregnant women, leading in a number of health-related consequences that impacted healthcare, including fetal and maternal ramifications. Infection by coronavirus 2 can harm placental tissue by causing a variety of alterations.

The majority of patients with SARS-CoV-2 are asymptomatic or have moderate symptoms related to upper respiratory infections that could sometimes escalate to severely sickness, injury of multi-organ, system failure, and death.

Evidence about the effects of maternal infection is growing. Emerging information points to an increase in the dangers associated with obstetrics, such as stillbirth, gestational diabetes, maternal problems, preterm births, hypertensive disorder, reduced intrauterine fetal growth, and a chance of neonatal impairments of development. Generally, it remains contradictory concerns regarding the possibility of vertical transmission.

Further analysis is needed on the placenta and its role in pregnancies with COVID-19 since impairment of placental function effects on fate of pregnancy. The reviewed studies referred to present of changes in the architecture of tissues as histopathological alterations accompanied coronavirus 2 outbreaks. The current review study can be a guide that helps doctors and researchers in the future to clarify effective plans in diagnosing and treating cases of this epidemic to prevent the risks it causes.

Keywords: *Placental Pathology, COVID-19, SARS-CoV-2*

INTRODUCTION

The angiotensin-converting enzyme-2 (ACE2) receptor is one of the main entry points for SARS-CoV-2 into host cells. Although this breathing virus mostly affects lung cells, causing acute respiration misery syndrome, it can also have an impact on other tissues that express ACE2. Unavoidably, effects of infection with SARS-CoV-2 on sensitive inhabitants, including pregnant women and unborn children, had attracted heedfulness on a global scale (Yan *et al.* 2020, Li *et al.* 2020).

The placenta can operate as both a friend and an enemy at the same time, with the ability to allow, inhibit, or termini the virus' growth and transmittable to fetus (Arora *et al.* 2017, Cardenas *et al.* 2010). It is widely known that the human placenta is crucial in controlling immunological reactions to a number of viral infections (PrabhuDas *et al.* 2015). Some viruses have the ability to breach the placental barrier and cause severe fetal abnormalities that can have long-term, pathological, and/or adverse postnatal repercussions (Lee *et al.* 2019). Malperfusion, thrombosis, and fibrin accumulation inside the placenta may all contribute to the risk of unfavorable outcomes for the fetus (Smithgall *et al.* 2020, Aghaaamoo *et al.* 2021).

Pregnant Women's Infection Symptoms

Depending on Clinical diagnosis for a variety of symptoms (bleeding, amniotic fluid leakage, uterine contractions), several deliveries were recorded for several cases of pregnancy and were later found to have SARS-CoV-2 infection, either for the first time or confirmed. Although there are many COVID-19 instances throughout gestation, congenital SARS-CoV-2 infections are uncommon. As a barrier, it is yet unknown how the placental functions stop the virus's transferring from mothers to their fetuses (Pacu *et al*. 2022).

SARSCoV-2 is connected to a maternal inflammatory response in circulatory path and mother-fetus interaction during pregnancy.Increased amounts of IgG and IgM were found in the peripheral circulation, and IgG was found in the neonatal cord blood after it passed through placental barrier via neonate's receptor of Fc (Flannery *et al.* 2021). The severity of COVID-19 can be exacerbated by maternal comorbidities such: advanced maternal age, diabetes mellitus, obesity, gestational hypertension and (Metz *et al.* 2022).

Mechanism of Defense in Placenta

In particular, examination of placenta can offer crucial information about changes to the structure human placenta, mechanism of transmission via maternal-fetal, and effects of organisms on placenta as a result of viral infection, including, vascular changes, abnormal inflammatory responses, necrosis and hemorrhagic lesions (Heerema-McKenney, 2018, Rosenberg *et al.* 2017). The placenta has the unusual ability to behave as both a friend and an enemy, permitting, preventing, or limiting the virus' growth and transmission to the fetus (Arora *et al.* 2017, Cardenas *et al.* 2010). It is widely known that the human placenta is crucial in controlling immunological reactions to a number of viral infections (PrabhuDas *et al.* 2015). Some viruses have the ability to breach the placental barrier and cause severe fetal abnormalities that can have long-term, pathological, and/or adverse postnatal repercussions (Lee *et al.* 2019).

Thrombosis, malperfusion and fibrin accumulation inside the placenta may all contribute to the risk of unfavorable outcomes for the fetus (Smithgall *et al.* 2020).

Additional information related to discovering the pathogenesis of infection, providing a safe pipeline of effective vaccines, developing of newly advanced and modulated controlling schedules, and existence of active diagnostic assays and therapies are necessary because the capability of the virus to dynamically and epidemiologically altered.

Pregnancy-related SARS-CoV-2 Transmission Route and Effects

Significant alterations are shown by placental pathology studies linked to SARS-CoV-2 infection. Notably, in a few investigations, persistent changes such histiocytic intervillositis have been found to be frequently transmitted from mother to child and to be associated with clinically adverse neonatal outcomes (Figure 1). It seems counterintuitive that, depending on the level of infection, infected placentas exhibit the majority of morphological alterations. In other instances, the morphology resembles that of patients who are not afflicted (Tosto *et al.* 2023).

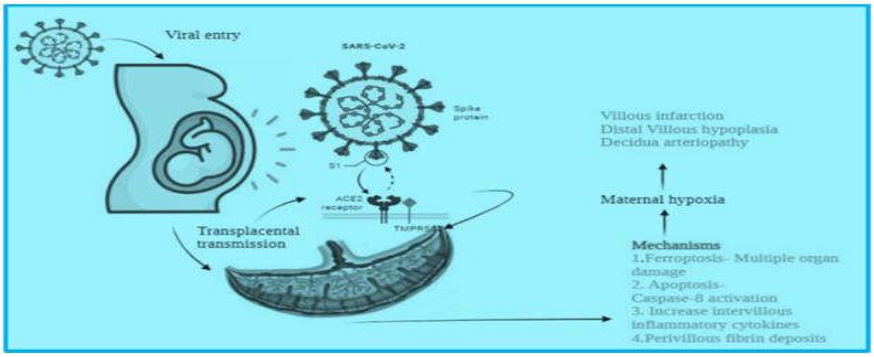

Figure 1: The effect of SAR-CoV-2 on placenta (Tosto *et al.* 2023)

The villi of women who needed respiratory support had a higher proportion of necrotic trophoblasts, demonstrating that the histological abnormalities seen in the placenta following SARS-CoV-2 infection are related to the severity of the disease (Meyer *et al*. 2022). The morphological and morphometrical analysis of the placenta makes use of advanced methodologies and techniques for placental investigation, such as transcriptome sequencing (RNA-seq), immunohistochemical studies, *in situ* hybridization, real-time quantitative PCR (RT-qPCR), transmission electrode microscopes and immunofluorescence techniques (AL-Shaeli et al. 2022, Meyer et al. 2022, Al-Hetty et al. 2023).

The evaluation of SARS-CoV-2 entrance parameters was the subject of several investigations. Invasion factors include molecules and receptors that can alter how receptive placenta is to SARS-CoV-2 invasion. Few studies had looked at how SARS-CoV-2 receptors, genes that code for proteins and proteases are localized in the placenta, suggesting that there is likely mutableness in each one third of pregnancy (Gesaka *et al*. 2022).

A crucial aspect of this infection is the expression of the ACE2 receptor, and two prerequisites appear to be required for transmission via transplacenta: (1) virus must enter the placentaand (b) ACE2 receptor must be expressed in the tissue of placenta. Tentatively, published results show the presence of SARS-CoV-2 in tissues of placenta (Gesaka *et al*. 2022, Patane *et al*. 2020).

In contrast, for the second condition, the results are still ambiguous (Li *et al*. 2020, Pique-Regi *et al*. 2020). Gengler *et al*. (2021) verified the presence ACE expression throughout the pregnancy, regardless of (SARS-CoV-2) status, by examining tissues of placenta at different gestational stages in negative and positive mothers to infection (Valdespino-Vázquez *et al*. 2021). The (TMPRSS2) furin and trans-membrane serine protease-2 aberrant expression levels were also proposed as main factors that might aid viral entrance (Essalmani *et al*. 2022, Tosto *et al.* 2023).

Histopathological alterations of placenta

Furin and TMPRSS2 inhibitors have been shown to be effective antivirals against SARS-CoV-2 because, according to Essalmani *et al.* (2022), they cooperate to promote viral entry and infectivity. Recent research has linked the insignificant expression of SARS-CoV-2 entry factors in the human placenta to the comparatively risk of low transmission of virus to placenta. The feto-placental unit is thought to be mostly resistant to SARS-CoV-2 infection, according to recent epidemiological data. These findings suggest that the virus reaches trophoblasts, but at lowered dose when compared to epithelial cells of lung that are receptive to it. Failure to activate the processes of post-entry, such as lysosomal de-acidification pathways or endosomal escape may restrict replication of SARS-CoV-2 in the placenta of human (Li *et al*. 2020).

It's interesting to note that Shook *et al*. (2021) looked at the possibility that fetal sex could mediate placental responses in (SARS-CoV-2) maternal infection. The authors specifically looked into whether fetal sex affected the expression of (TMPRSS2) and ACE2 in placenta. Finally, no effect of status of maternal SARS-CoV-2 or fetal sex on ACE2 was seen. Males but not females showed a substantial correlation between TMPRSS2 expression and ACE2 expression (Shook *et al*. 2021). Understanding the impact of sex ov viral transmission depends in part on the detection of a putative sexually dimorphic response to maternal SARS-CoV-2 infection in placental TMPRSS2 levels. The male placenta protective compensatory strategy is reflected in decreased TMPRSS2 concentrations in existence of SARS-CoV-2 infection in mother (Shook *et al*. 2021).

It has also been hypothesized that the expression of CD47, HLA G, CD26, and CD56 in syncytiotrophoblast cells may act as alternative SARS-CoV-2 entrance receptors (Dong *et al*. 2021, Schiuma *et al*. 2023). In a recent studies by Dong *et al.* (2021), there was no lineal evidence of transmission of virus to infants, but there was a difference in the expression of CD147 and ACE2 in a number of pregnants with SARS-CoV-2 in comparison with those does not infected (Dong *et al*. 2021). Additionally, odd escape behaviors the SARS-CoV-2 virus occasionally displayed correlated with the production of immunotolerogenic protein human leukocyte antigen (HLA)-G. Pregnancy-related HLA-G placental expression is peculiarly changed at higher concentration of molecule during the earlier third stage of pregnancy and a decline as labor approaches to support the normal inflammatory response (Tosto *et al.* 2023).

Conclusion

Host cells are attacked by SARS-CoV-2 through the angiotensin-converting enzyme 2 (ACE2) receptor, including respiratory tract, digestive system, cardiovascular system. The effects of coronavirus infection on vulnerable communities as pregnant women, newborn babies, and the elderly have received great attention worldwide. The current survey, which dealt with research that coincided with the pandemic, indicated that there were pathological changes in the placenta tissue in pregnant women.

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