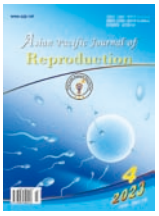

Review Article

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Effects of SARS-CoV-2 infection on pregnancy outcome: An overview

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may have harmful effects on expectant moms, labor, and newborns born to infected mothers. There is a risk of the initiation of pregnancy with infection. Even if the gametes are non-infected, pregnancies could be exposed later for infection by coronavirus. Investigations of COVID-19 during pregnancy highlighted the non-transmission or surprising transmission of SARS-CoV-2 to the offspring. However, other studies have exhibited the potential mother-to-fetus transmission. In this way, unanswered concerns about SARS-CoV-2 fetal transmission and the particular interface(s) controlling its pathogenesis throughout pregnancy persist. This review focuses on the potential effects of SARS-CoV-2 on vertical transmission, as well as the influence of the virus on pregnancy and placenta.

KEYWORDS: SARS-CoV-2; Hazard effects; Pregnancy; Placenta

1. Introduction

The novel infectious agent responsible for coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused over 750 million cases and over 6.5 million deaths worldwide according to the latest update of the World Health Organization (WHO)[1]. WHO declared a global pandemic of COVID-19 in March 2020, caused by the SARS-CoV-2[2]. 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[3]. Evidence suggests that pregnant women with COVID-19 are more susceptible to severe disease with a higher risk of preterm birth[4,5], as well as higher risk of maternal and/or fetal death[6,7]. Due to COVID-19, governments all over the world just announced the most extensive limitations on individual freedom in modern history. The marked expansion in COVID-19 infections promotes the possibility of massive hospitalizations that no medical care framework in the world can control. With a strong agreement, the critical suggestions from specialists include cancellation of all embryo transfers, whether fresh or frozen, cancellation of elective surgery, cancellation of non-urgent diagnostic procedures, and suspension of new fertility treatments such as ovulation induction, intrauterine insemination, and *in vitro* fertilization, as well as non-urgent gamete cryopreservation[8]. Patients who are "in-cycle" at the moment or who need urgent fertility preservation owing to cancer treatment are the exceptions.

2. Methods

An extensive search of studies published until 2023 was carried out in the databases of PubMed, Science Direct, EBSCO, Scopus, Sage Journals, and Google Scholar. The search was conducted with various combinations of the following keywords: 'SARS-CoV-2', 'Acute Respiratory Syndrome Coronavirus 2', 'hazard effects', 'pregnancy', 'placenta', 'World Health Organization'. Articles were evaluated based on their title or abstract, and relevant original research studies and review articles were included in this review. Emphasis was placed on studies addressing the following topics: SARS-CoV-2, SARS-CoV-2 in reproduction, vertical transmission of SARS-CoV-2, SARS-CoV-2 effects on pregnancy, SARS-CoV-2 effects on the placenta and placental pathology after SARS-CoV-2 infection. Articles were excluded if they were not written in English.

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3. Pathogenesis of SARS–CoV–2 in reproduction

According to Lu *et al*[9], SARS-CoV-2 shares around 79% genetic similarity with SARS-CoV and approximately 50% with the Middle East respiratory syndrome coronavirus. According to homology modelling, SARS-CoV-2 and SARS-CoV share a receptor-binding domain structure, which raises the possibility that the pathogenesis of COVID-19 infection and SARS-CoV infection may be comparable[9,10]. These coronaviruses share striking similarities in their spike (S) protein 3D structures, which are thought to have a high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor found on human cells. Through single-cell RNA sequencing data analyses, Zou *et al*[11] identified specific cell types that are susceptible to SARS-CoV2 infection and may be connected to the reported clinical symptoms of SARS-CoV infection. These organs at risk include the lung, heart, esophagus, kidney, bladder, and ileum. Furthermore, coronavirus cell entrance involves more than just the viral spike protein binding to the cellular receptor, since S protein priming by host cell proteases also contributes to coronavirus cell entry (Figure 1).

Hoffmann *et al*[12] showed that SARS-CoV-2 requires the serine protease [transmembrane cellular protease serine 2 (TMPRSS2)] for S protein priming and the SARS-CoV receptor ACE2 for entrance. A plasma membrane-anchored serine protease that is involved in proteolytic cascades relevant to the proper physiologic function of the prostate is encoded by the prostate-specific and androgen response gene TMPRSS2[13]. Data from high-throughput single-cell RNA sequencing suggested that human testes may be at risk of SARS-CoV2 infection[14,15]. However, the sequencing depth of high-throughput single-cell RNA sequencing restricts its ability to be interpreted.

Inconsistent results were reported by different studies concerned with investigating the role of male reproductive system in carrying and transmission of SARS-CoV-2. These contradictory results are related to the existence of SARS-CoV-2 in the semen of men with COVID-19[16–18]. The timing of the examination, the sensitivity of the test, potential contamination, patient age, *etc*. may all contribute to variations in these investigations. The male reproductive system needs to be carefully examined further for any potential infections.

For more details on the mechanistic understandings of viral entrance and the effects of viruses on reproduction, ACE2 and TMPRSS2 expression profiles in human spermatogenic cells, follicular cells, and preimplantation embryos were the focus of the investigation carried out by Cheng *et al*[19]. The results showed that during gametogenesis in spermatogonia, ACE2 is mainly expressed and its expression is not restricted to spermatogonia only but it also includes oocytes of antral follicles, granulosa cells of antral follicles and pre-ovulatory follicles. In contrast, these cells (spermatogenic cells, oocytes or granulosa cells) did not have expression of TMPRSS2. In addition, expression of ACE2 in preimplantation embryos occurs first in early embryos before the eight-cell stage and in the trophectoderm of late blastocysts, while expression of TMPRSS2 occurs first in the late blastocyst stage. The significant co-expression of both ACE2 and TMPRSS2 occurs in the trophectoderm of late blastocysts in all the above cell types (Figure 2). Therefore, the authors recommend that the opportunity of SARS-CoV-2 transmission to offspring through gametes is very low and the transmission occurs through the trophectoderm of late blastocysts, which are more susceptible to SARS-CoV-2. Thus, they suggest that fertility preservation for patients suffering from coronavirus infection is relatively safe and rational. Also, suggestions involved contraindication of embryo cryopreservation and embryo transfer into healthy recipient mother

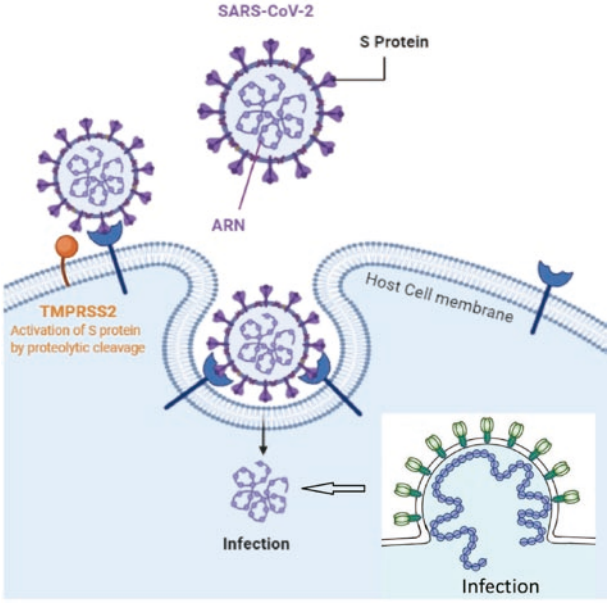

Figure 1. The role of spike (S) protein priming by host cell proteases in coronavirus cell entrance. TMPRSS2: transmembrane cellular protease serine 2.

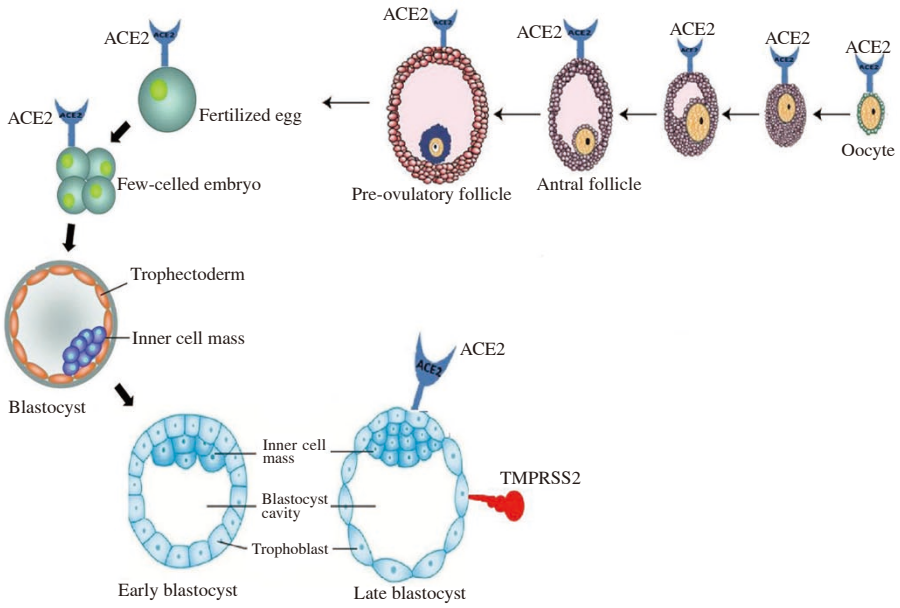

Figure 2. Angiotensin-converting enzyme 2 (ACE2) expression during gametogenesis in spermatogonia, oocytes of antral follicles, granulosa cells of antral follicles and pre-ovulatory follicles. TMPRSS2: transmembrane cellular protease serine 2.

through blastocyst stage and should occur through cleavage stage instead. Besides, during fetus development, clinical examination and animal models for further evaluation are required as it is noticeable that infection of trophectoderm in the blastocyst may influence fetus development. The authors observed that in humans, rhesus monkeys and mice, the co-expression of ACE2 and TMPRSS2 are totally different. Therefore, evaluating the transmission risk of SARS-CoV-2 in reproduction through animal models will have significant limitations.

4. Vertical transmission of the virus

SARS-CoV-2 infections in pregnant women and the likelihood of vertical transfer of the virus to the fetus are hotly contested[20,21]. ACE2 is found on the host cell membrane, which facilitates the entry of SARS-CoV-2 into target cells. The TMPRSS2 primes the viral spike protein, allowing membrane fusion and viral entrance[12,22]. It was reported that ACE2 has a more limited distribution than TMPRSS2 which may recommend that ACE2 may be a limiting factor for viral entry[23].

According to studies thus far, pregnant women who contract SARS-CoV-2 do not have higher rates of morbidity or fatality than women who do not become pregnant[24–26]. It was shown by initial studies of corona virus carried out during gestation that SARS-CoV-2 is not transmitted or unusually transmitted to the fetus[3,25]. There was no evidence of mother-to-child transmission, according to Chen *et al*[25]. The co-transcription of ACE2 and TMPRSS2 is weak, according to the most recent research by Pique-Regi *et al*[27], which does not support the vertical transmission of SARS-CoV-2 at any stage of pregnancy. Therefore, based on the most recent clinical data, it seems unlikely that SARS-CoV2 will infect the fetus. The majority of the literature has described healthy neonates born to mothers with COVID-19, while clinical symptoms in neonates due to SARS-CoV-2 exposure are still being fully characterized[24,25,28,29]. However, with cohort studies revealing a range of 0%-4.5%[30,31], some researches show that there is a low rate of positive SARS-CoV-2 testing in infants born to mothers with COVID-19. Even though more obstetrical and neonatal facilities are embracing universal testing, these rates have remained low. Other publications indicated that after detection of immunoglobulin M (IgM) antibodies[32] or positivity of reverse transcriptase-polymerase chain reaction (RT-PCR) in newborns a few hours after birth[33–35], the probable transmission of the virus from the mother to her child may occur. Dong *et al*[32] announced that a mother with COVID-19 gave birth to a child who had elevated IgM antibody level two hours after birth and therefore encouraged the probable of mother-to-child vertical transmission. Nonetheless, the incidence of this condition in a single case and no confirmatory tests such as PCR to perform on the amniotic fluid or placenta represents a limitation of this report. In addition, till the beginning of 2021, there are yet few published data on the co-expression of TMPRSS2 and ACE2 in preimplantation embryos or the female reproductive system. When assessing the safety of assisted reproductive technologies, it is crucial to consider the danger of SARS-CoV2 infection in human reproductive cells and early embryos for potential viral infection and transmission. Moreover, another study illustrated that tests of viral RT-PCR in five cases of fetal deaths gave positive results in one case in the amniotic fluid and in two cases in the placenta. In spite of studies that expose this indirect evidence of SARS-CoV-2 vertical transmission, no study has yet evidenced in a comprehensive manner the presence of the virus in fetal tissues. Because of this, Marinho *et*

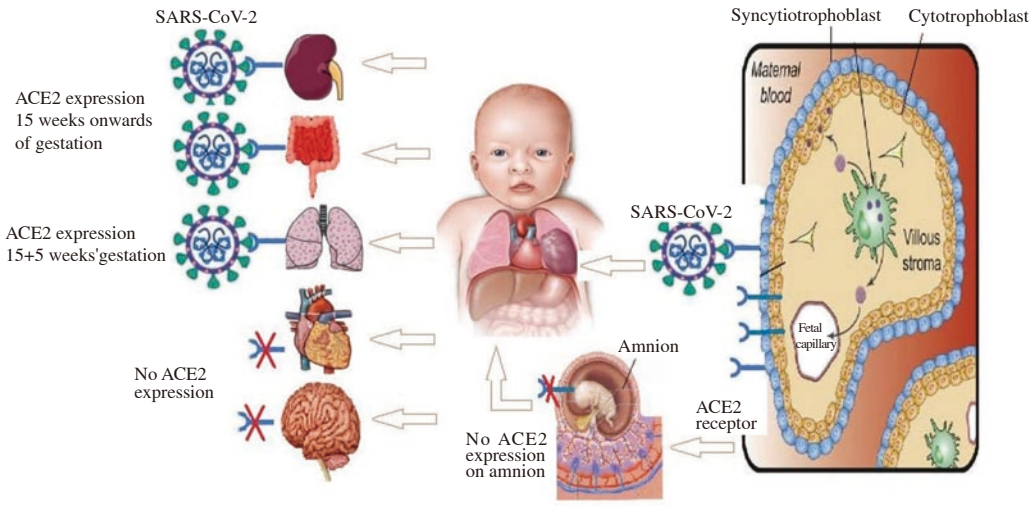

Figure 3. Angiotensin-converting enzyme 2 (ACE2) expression in the placenta and fetal organs from pregnancies infected with SARS-CoV-2.

al[36] reported a confirmed mother-to-child transmission of SARS-CoV-2, illustrating the virus's pervasive detection in the placenta, umbilical cord, and various fetal tissues. Additionally, examinations of fetal-placental magnetic resonance imaging (MRI) and placenta histology revealed thromboembolic involvement in the placenta, which was suggested as the most likely reason for fetal death. This patient's subsequent thrombophilia screening revealed no significant risk factors, indicating that infection with the novel coronavirus was the primary cause of placental thromboembolic consequences. There are still unanswered questions regarding SARS-CoV-2 fetal transmission[26,30,37–42] as well as the specific interface(s) governing its pathogenesis during pregnancy. For COVID-19 testing, established pregnancy transmission pathways such as placental, intrapartum (such as blood, vaginal secretions), or postpartum (such as lactation) intervals are all necessary[43,44].

5. The effect of the virus on pregnancy and the placenta

Significant changes to the placental parenchyma, especially in the villous and subchorionic compartments, have been described in cases of SARS-CoV-2 maternal infection on a consistent basis[42,45–47]. In addition, the most frequent pathological diagnoses obtained from histopathological studies of placentas include fibrosis, maternal vascular malperfusion, and intervillous thrombi[48–51]. Moreover, others reported that inflammatory lesions such as chronic histiocytic intervillositis, villitis, funisitis, and chorioamnionitis were also found[52]. This indicates that significant parenchymal changes occur in the placenta secondary to maternal COVID-19 infection. These findings illustrate that there is an organ-specific antiviral mechanism of SARS-CoV-2 at the maternal-fetal interface that can be expected from the findings which indicate that in most pregnancies, SARS-CoV-2 transmission to the fetus is avoided.

Some authors ratify that the placental pathology can be used to manifest the virus transmission through the maternal-placental interface. Therefore, in cases where there is an infected maternal-fetal dyad, the findings of placental pathology are different from those where there is not an infected fetal or neonatal dyad[52]. Thus, Schwartz and Morotti[52] carried out a study with an aim to diagnose transplacental SARS-CoV-2 transmission between infected maternal-neonatal dyads through placental pathology criteria. Molecular identification of the virus on the fetal side of the placenta was the basis of these criteria, such as application of immunohistochemistry for demonstrating viral antigens or using RNA in situ hybridization or RNAscope methods for detection of viral nucleic acid. Results showed that transplacental transmission of the virus was the route through which several neonates gained their COVID-19 infection in utero from an infected mother[45,53–55].

For more details, Schwartz and Morotti[52] tried in a communication to provide an analysis of the spectrum of pathology findings from COVID-19 infected pregnant women depending on the infection status of their infants. The authors also suspect that the placenta, in terms of placental and fetal infection with SARS-CoV-2, is one of the risk factors responsible for developing intrauterine transplacental fetal infection. This suspect forced the authors to examine the placental pathology. According to the data, there is a considerable variation in the range of pathology findings in the placentas of pregnant COVID-19-positive mothers and neonates who are not infected. On the contrary, mononuclear cell inflammation of the intervillous space, termed chronic histiocytic intervillositis, associated with syncytiotrophoblast necrosis, were the prominent findings in the placentas from infected maternal-neonatal dyads. These findings confirm the previous recommendations of transplacental viral transmission. From all of the previous, we can conclude that the presence of chronic histiocytic intervillositis and trophoblast necrosis can be risk factors for SARS-CoV-2 placental infection and maternal-fetal viral transmission.

Taglauer *et al*[56] provided a different point of view and suggested

that ACE2 and TMPRSS2 are located in specific anatomical regions of the placenta and that SARS-CoV-2 invades the villous placental compartment regardless of fetal transmission. They examined the relative expression of the SARS-CoV-2 spike glycoprotein (CoV2 SP), ACE2, and TMPRSS2 in these tissues using quantitative immunofluorescence. Results illustrated that COVID-19 positive pregnancies expressed the presence of CoV2 SP within the villous placenta with and without evidence of fetal transmission. In addition, they showed that comparison between ACE2 expression and TMPRSS2 reveals the predominance of ACE2. Furthermore, a crucial physiological link between mother and fetus, the outer syncytiotrophoblast layer of placental villi, is where CoV2 SP and ACE2 are largely located.

Another study performed by Faure-Bardon *et al*[57] hypothesized that the relatively low ACE2 expression in the placenta and organs aimed by the virus might relate to the low incidence of perinatal infection. Thus, the authors carried out a study at various gestational ages with an aim to assess ACE2 protein expression in both placentae and fetal organs obtained from pregnancies free from SARS-CoV-2 infection. Moreover, the authors collected a placenta from a pregnant woman who was infected with SARS-CoV-2 and checked it to determine the expression of ACE2 in order to determine whether expression was altered in the context of SARS-CoV-2 infection (Figure 3). Results showed that ACE2 expression was detected in different organs such as fetal kidney, rectum and ileum samples from 15 weeks onwards and in the pediatric controls. However, other organs, such as fetal lung samples at 15+5 weeks' gestation hardly showed this expression. Besides, only type-2 pneumocytes in the pediatric controls showed the expression. In contrast, the cerebral ependymal or parenchymal tissues and cardiac tissues do not expose ACE2 expression. ACE2 was expressed in placental syncytiotrophoblast and cytotrophoblast samples, however not within the amnion, from 7 weeks onwards. Therefore, we can conclude that ascending vertical transmission may arise, in particular after rupture of the amniotic membranes.

This conclusion originated after detection of the absence of ACE2 from the amnion. The proposed risk of congenital deformity and the morbidity of perinatal infection are proven by the lack of ACE2 expression in certain fetal organs, including the brain, lungs, and heart. Nevertheless, in order to achieve protection against additional risks that may arise from SARS-CoV-2 infection, follow-up studies of infected pregnancies should be conducted. These studies should focus on fetal morbidity caused by the placenta, including prematurity and growth restriction related to chorioamnionitis.

6. Conclusions

Pregnancies could suffer from infection of SARS-CoV-2, and the chance of vertical transmission of the infection to the fetus is the subject of important discussion. In this way, unanswered concerns about SARS-CoV-2 fetal transmission and the particular interface(s) controlling its pathogenesis throughout pregnancy persist. Placenta is one of the recognized pregnancy transmission mechanisms that needs further COVID-19 testing. Finally, the potential effects of the virus on vertical transmission, as well as the influence of the virus on pregnancy and placenta, are some of the important topics that need a lot of research to confirm findings.

Conflict of interest statement

The author declares that he has no competing interests.

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Author's contributions

Yahia A. Amin conducted a literature search and wrote a rough draft. The study was conceptualized, planned, and conducted by Yahia A. Amin. He also created figures and edited and revised the article.

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