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Review

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Review

Influence of SARS-CoV-2 during pregnancy: a placental view

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Abstract

Since the beginning of the current coronavirus outbreak (COVID-19), there has been great concern over a disease that has spread rapidly in several countries worldwide, with the result of several deaths, including deaths of pregnant women. Therefore, the aim of this study was to conduct a literature review on placental changes in infected pregnant women and/or asymptomatic carriers of COVID-19 during pregnancy, aiming at the possible vertical transmission. A systematic collection was carried out on the effects of that COVID-19 can cause directly and/or indirectly to pregnancy and the placenta in the following databases: Pubmed, Science Direct, Scielo, Lilacs, and Web of Science. For search, the following descriptors were used: placenta, pregnant woman, COVID-19, maternal–fetal. The results indicate transplacental transmission in some cases reviewed in many reports from this study. The presence of the virus was seen in the amniotic fluid, umbilical cord, and peripheral blood. Finally, pathological studies suggest that there are morphological changes related to infection in the placentas. We can conclude that, based on the researched material, there is little evidence of transplacental vertical viral transmission and its respective morphological changes related to viral infection in the placenta.

Summary sentence

There is small evidence of transplacental vertical viral transmission and its respective morphological changes related to viral infection in the placenta.

Key words: COVID-19, pregnancy, placenta, maternal–fetal.

Introduction

A cluster of pneumonia cases, caused by a newly identified β-coronavirus, occurred in December 2019, in Wuhan, China [1]. Thus, a new type of disease appears called COVID-19 from the family of Coronavirus. The phylogenetic tree of the virus showed that the virus clustered significantly with the Coronavirus' sequence similar to the SARS-CoV of bats, which was isolated in 2015. The structural analysis of the virus revealed a mutation in the glycoprotein Spike and in the protein nucleocapsid. This information suggest that COVID-19 is a different coronavirus compared to SARS, likely transmitted from bats to another host which could infect humans [2].

The coronaviruses are RNA viruses that cause respiratory infections. This RNA virus affects several species, including birds and mammals [3]. That can infect humans and animals, and the infection can affect the respiratory system, gastrointestinal, and central nervous system. These factors lead to the virus becoming more and more virulent [4]. It is believed that the seasonal coronavirus is generally associated with flu-like syndromes. Also, it is easily transmitted and affects mainly patients with chronic disease. Patients with pulmonary deficiency, chronic renal problems, diabetes, hypertension, heart disease, users of corticosteroids or immunosuppressive drugs, smokers and the elderly, are the population most susceptible to pneumonia [1, 5]. The weakened immune system, circulatory problems, and the fragility of the lungs, promote the aggressiveness of the infection [6].

Due to its characteristics, the disease quickly spread, causing an epidemic in China, after 3 months, it became a pandemic [7]. On 16 February 2020, the World Health Organization (WHO) [8] informed that, globally, there were 51 857 confirmed cases in 25 countries. On March 1, in the same year, a total of 79 968 cases of COVID-19 were confirmed in mainland China, including 2873 deaths.

About the virus, diversity of viral variants has been found in some infected patients, suggesting a fast evolution of SARS-CoV-2. This is because it is an RNA virus, the risk of active recombination and mutations attributed to RNA-dependent RNA polymerases happen faster [9]. The presence of the SARS-CoV protein and its RNA were detected only in ACE2+ cells (enzyme which convert Angiotensin 2), both in lungs and other organs, indicating that cells expressing ACE2 are the main assets of SARS-CoV infection in humans, this functional receptor of SARS-CoV [10] is reported to be highly present in renal tubular cells, Leydig cells, and seminiferous duct cells in the testis [11].

The SARS-CoV receptor is widely disseminated in specific cell types in the maternal–fetal interface and fetal organs. Therefore, vertical transmission and placental dysfunction/abortion caused by SARS-CoV-2 need to be investigated more carefully in clinical practice [12]. Although the placenta allows the exchange of materials between mother and fetus, there is no direct passage between the maternal and embryonic circulation. This exchange of materials is done by diffusion and active transport. However, the molecular exchange pathways between mother and fetus may also allow the passage of some toxic substances and pathogens, such as viruses that can cause serious problems to the fetus [12].

Epidemiological overview of people infected with SARS-CoV-2

After a 3-month period of emergence, COVID-19 has become a worldwide pandemic [7]. The virus first appeared in Wuhan, China, in December 2019 and quickly spread across the world, infected 48 539 872 people and caused 1 232 791 deaths in 215 countries, and the infection will still spread until the time of vaccination [13].

China reported its first case on 31 December 2019, with a peak of cumulative cases over an 8-week interval and therefore a plateau. Italy followed the same path after ~11 weeks and the USA after ~13 weeks (from the first case in China). In India, cases increased after ~12 weeks from the first case in China and, although cases and deaths are still increasing in the USA and India, Italy is already witnessing a decrease in new daily cases [14].

Between the states in Brazil, in 13 January 2021, it was registered São Paulo in first place of contamination by COVID-19, with 1 577 119 confirmed cases and 48 985 deaths. In second, Minas Gerais were 611 152 confirmed cases and 12 894 deaths; follow by Bahia, where there were 518 955 cases and 9512 deaths [15].

SARS-CoV-2 and pregnants

Due to the presence of physiological changes, call immunological, and cardiopulmonary changes, the pregnant woman is more susceptible to respiratory and systemic complications in infections caused by the virus [16]. In general, the body of the pregnant woman already shows physiological changes, which leads to a predisposition for possible severe infections, including respiratory [17]. In addition, anatomical changes reduce the tolerance of pregnant women to hypoxia [18]. The main anatomical changes existing in the physiology of pregnant women are: increase in the transverse diameter of the rib cage, elevation of the diaphragm, changes in lung volumes, vasodilation in the mucosa, and changes in cell-mediated immunity. So far, there is no evidence that pregnant women are more affected or have more complications than others [19].

The Ministry of Health of Brazil (2020) [15] released technical note No. 12/2020-COSMU/CGCIVI/DAPES/SAPS/MS, which reports about the COVID-19 infection and the risks to women in the pregnancy–puerperal cycle. Because of the severity of the pandemic, the technical note reports that, based on past world experiences in other respiratory infections in the pregnancy–puerperal cycle, and deaths in pregnant/postpartum women by COVID-19 in the country, it is suggested that it is vigilance and precautionary measures in relation to pregnant women and women who have recently given birth.

In the publications of [19, 20], the authors describe in 21 pregnant women a premature rupture of membranes, preterm delivery, fetal tachycardia, non-tranquilizing fetal status, fetal death, and high number of cesarean sections. It is important to know the high number of cesarean sections was due to clinical severity. However, there was no maternal death.

The study by [18] was about 43 cases. These cases followed classification of severity as proposed by Wu and McGoogan. In this study, it found that among all SARS-CoV-2 positive pregnant and postpartum patients, 86% of the patients coursed the disease in a mild form, 9.3% developed a severe disease, and 4.7% were considered critically-ill patients. The study by [19] carried out a systematic review of 107 other cases of COVID-19 in pregnant women. Their results showed no maternal mortality and only 3% of them were admitted to the ICU. Its findings are compatible with data from [5] compared to the evolution of the disease among non-pregnant adults, where 80% presented the disease in a mild disease, 15% in a severe disease, and only 5% as being in a critical disease.

The Breslin et al. [18] conducted a case study of 43 pregnant women confirmed with COVID-19 from two hospitals in New York City in March 2020. Fourteen (32.6%) patients had viral symptoms associated with COVID-19, being identified after the universal test for all hospital obstetric admissions. Another relevant information is that of the 43 pregnant women, 14 (32.5%) developed the signs and/or symptoms of the infection during childbirth. About the remaining 29 (67.5%) pregnant women, only three required prenatal admission due to viral symptoms and, one patient, presented 6 days after delivery a worsening of the respiratory state which required oxygen support.

In total, 46 pregnant patients from a retrospective study of pregnant women with a severe respiratory infection by coronavirus-2 (SARS-CoV-2) confirmed in the laboratory from six hospital systems in Washington State between 21 January 2020 and 17 April 2020, with SARS-CoV-2 infection were identified in hospital systems that captured 40% of births in Washington State. Almost all pregnant women with SARS-CoV-2 infection were symptomatic (93.5%, $n = 43$) and most were in the second or third trimester (43.5%, $n = 20$ and 50.0%, $n = 23$, respectively). The symptoms resolved in a median of 24 days (interquartile range 13–37). Seven women were hospitalized (16%), including one lead to the intensive care unit. Six cases (15%) were classified as severe COVID-19 disease, with almost all patients being overweight or obese before pregnancy, asthma or other comorbidities. Eight deliveries occurred during the study period, including premature delivery at 33 weeks to improve lung status in a woman with Class III obesity. There was stillbirth of unknown etiology [21].

The Chen et al. [19] evaluated a total of nine pregnant patients, positive for SARS-CoV-2, who had a cesarean section in the third trimester. Seven patients had fever. Other symptoms, including cough (in four out of nine patients), myalgia (in three), sore throat (in two), and malaise (in two), were also observed. Fetal distress was monitored in two cases. Five of the nine patients had lymphopenia ($<1.0 \times 10$ cells per L). Three patients showed an increase in aminotransferase concentrations. None of the patients developed severe COVID-19 pneumonia or died on 4 February 2020. Nine live births were registered. Neonatal asphyxia was not observed in newborns. All nine live births had an Apgar score of 1–8 min and an Apgar score of 5 min of 9–10. Samples of amniotic fluid, umbilical cord blood, smear of the neonatal throat, and breast milk from six patients were tested for SARS-CoV-2, and all samples were negative for the virus.

Influence of SARS-CoV-2 infection on placentas

In mammals, most embryonic losses occur during early pregnancy, probably due to major developmental events such as embryonic organogenesis and placental development, a process known as placentation. This includes extensive angiogenesis in both the placenta and the fetus, accompanied by a marked increase in uterine and umbilical blood flows. These events provide the developing concept with an ideal uterine environment to meet its metabolic changes and probably also influence the rate of physiological exchanges between the maternal and fetal systems [20].

The Jing et al. [21] reviewed the literature and reported the distribution and function of angiotensin 2 (ACE2) in the female reproductive system, looking to clarify the potential damage of COVID-19 to female fertility, since the (ACE2) converting enzyme is now confirmed as a SARS-CoV-2 receptor and plays essential roles in infection and transmission. The evidence so far suggests that (ACE2) is highly expressed in the ovary, uterus, vagina, and placenta. Therefore, it is believed that, beyond transmission by droplets and contact, there is also the possibility of mother-to-child and sexual transmission. Ang II, ACE2, and Ang- (1–7) regulate follicular development and ovulation, modulate angiogenesis, and luteal degeneration and also influence regular changes in endometrial tissue and embryonic development. Considering these functions, COVID-19 can disrupt female reproductive functions by regulating ACE2 [21].

The study by [12] revealed that the SARS-CoV-2 ACE2 receptor was widely spread on specific cell types of maternal–fetal interface and fetal organs. The results revealed that ACE2 was highly expressed in maternal–fetal interface cells, including stromal cells and perivascular cells of the basal decidua and cytotrophoblast and syncytiotrophoblast of the fetal placenta. Meanwhile, ACE2 has also been expressed in cell-specific human fetal heart, liver, and lung, but not in the kidneys. And in a study analyzing the fetal and postnatal lungs of mice, was found that ACE2 was altered over time, and extremely high in neonate mice on the first–third day postnatally. Although previous clinical studies have not observed vertical transmission of SARS-VOC-2 in the limited cases, this phenomenon still needs to be investigated more carefully in clinical practice [12].

Morphological aspects of SARS-CoV-2 infection in the placentas and their vascularization

The first visualization of SARS-CoV-2 in the human placenta was done by Algarroba et al. [22] through the TEM, they were able to identify virions that invade syncytiotrophoblasts in placental villi. Also, they identified SARS-CoV-2 virions in the placental villi in fibroblast cell processes. Fibroblasts can take the form of myofibroblasts as a result of the response to injury or inflammation, in this case by SARS-CoV-2 [22].

A study by [23] with 12 patients from southern China with SARS from five public hospitals in Hong Kong, evaluated the histopathology of these patients' placentas. All placentas had a weight below the fifth percentile for pregnancy, with a weight deficiency of 8–47%. Three placentas showed normal histopathological results. Two placentas of pregnancies complicated by intrauterine growth restriction showed avascular fibrotic terminal villi with thrombotic vasculopathy in some stem villi. The percentage of infarcted placental tissue was estimated to be around 10%. None of the placentas showed chorioamnionitis, funisitis, villitis, viral inclusion, or other characteristics of the infection [23].

The Ng et al. [24] evaluated seven placentas. They were indicated as P1 to P7 in the chronological order in which the placentas were received. All patients were in the third trimester at the time of SARS-CoV diagnosis, except P6 and P7. The placentas of two women infected with SARS in the first trimester were normal. In three placentas were in the acute stage of SARS, there were increases in subcutaneous or sub-chorionic fibrin that may be related to disorders in the blood flow of the maternal placenta due to hypoxic respiratory disease. Extensive fetal thrombotic vasculopathy (FVT) with clearly demarcated areas of fibrotic avascular villi was observed in the placentas of two SARS-infected patients in the third trimester. Both pregnancies showed intrauterine growth retardation, oligohydramnios and small newborns for pregnancy period. The etiology of FVT may be related to the SARS thrombotic tendency or placental hypoxia [22]. In pregnant women affected by COVID-19, a fetal growth restriction would be reasonable, given the acute and chronic placental changes seen in SARS pregnancies, with placental

detachment also being noted, which was observed in a case affected by Middle East respiratory syndrome (MERS) [25].

The Mulvey et al. [26] analyzed the placental pathology of five full-term births in patients with COVID-19, which is increasingly being recognized as a systemic syndrome of thrombotic and microvascular injury that may have its roots in complement activation. All five exhibited histology indicative of poor fetal vascular perfusion characterized by focal avascular villi and thrombi in larger fetal vessels. The deposition of vascular complement in the placentas was not abnormal and the staining for viral RNA and viral peak protein was negative. Although all cases resulted from healthy deliveries, these findings indicate the systemic nature of SARS-CoV 2 infection. The discovery of vascular thrombosis without complement deposition may reflect the systemic nature of the COVID-19 procoagulant effects not related to systemic complement activation.

Three placentas from pregnant women with confirmed COVID-19 infection, all in the third trimester with emergency cesarean section. There were different degrees of fibrin deposition in and around the villi, with increases in local syncytial knots in the three placentas. In one case, the placenta showed the concomitant morphology of chorionic hemangioma and the other with massive placental infarction. There are no pathological changes in villitis and chorioamnionitis were observed in our observation of three cases. All samples from three placentas were negative for the virus. Pathological study suggests that there are no morphological changes related to infection in the three placentas [27].

One study analyzed 38 pregnant women with COVID-19 and their newborns in China to evaluate the effects of SARS-CoV-2 on mothers and babies, including clinical, laboratory and virological data, and the maternal–fetal transmissibility of the virus. Similar to pregnancies with SARS and MERS, there were no confirmed cases of intrauterine transmission of SARS-CoV-2 from mothers with COVID-19 to their fetus. All neonatal samples tested, including some placentas, were negative by rt-PCR for SARS-CoV-2 [28]. A woman with COVID-19 gave birth to a baby in the 35th week of pregnancy by cesarean section. The baby was negative for SARS-CoV-2 as were samples of serum, urine, feces, amniotic fluid, umbilical cord blood, and placenta and samples of breast milk; however, the sputum of the mother was positive for the virus [29]. Thirty-one pregnant women infected with COVID-19 have been reported. No COVID-19 infections were detected in their neonates or placentas [30]. Dashraath et al. [31] corroborates that there was no vertical transmission in his study, in which the results of 55 pregnant women infected with SARS-CoV-2 and 46 neonates, demonstrate the absence of viral isolates in the amniotic fluid, umbilical cord blood, milk, and neonatal throat swabs. Limited data obtained from cases of pregnant women with COVID-19 suggest that transplacental transmission is unlikely in late pregnancy close to delivery, as the virus was not identified in the amniotic fluid, placenta, breast milk of these mothers, or in the nasal secretions of their newborns [32].

A case of neonatal COVID-19 infection in China was reported with a positive test by the RT-PCR test 36 h after birth. However, it has not confirmed whether the case is a mother-to-child vertical transmission, since the results of nucleic acid detection of umbilical cord and placenta blood have tested negative [33]. One newborn was positive, but viral tests for placental nucleic acid and cord blood, in this case, were negative [19, 27].

On the contrary, in the study [32] of the 32 COVID-19 positive pregnant patients who gave birth, placental membrane of 11 patients or swabs were analyzed. Three of the 11 swabs were positive. None of the babies tested positive for SARS-CoV-2 on days 1–5 and none showed symptoms of COVID-19 infection.

The Vendola et al. [35] reported the presence of viruses in two clinical cases. In the first case, the test was positive in the umbilical cord and in the newborn's peripheral blood shortly after delivery. In the second case, the umbilical cord, the peripheral blood, and the amniotic fluid were tested positive, thus confirming maternal vertical transmission. Given the mixture of fluid and maternal and fetal tissue at the time of delivery, the origin of the detected SARS-CoV-2 RNA is unclear. It may represent contamination by maternal blood, amniotic fluid or COVID-19 infection of the membranes and amniotic sac. For babies delivered vaginally, contamination with vaginal secretions is also a possible source, although previous studies on vaginal secretions have not shown the presence of COVID-19 [34].

Conclusion

We can conclude that, based on the researched material, there is small evidence of transplacental vertical viral transmission and its respective morphological changes related to viral infection in the placenta.

Conflict of interest

The authors declare that they have no competing interests.

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