EFFECTS OF COVID-19 ON PREGNANCY AND INFLUENCE OF PREGNANCY ON THE DISEASE

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ABSTRACT

COVID-19 has been considered a systemic disease caused by the new coronavirus, which raises concerns about the consequences for the health of the pregnant woman and the conceptus. Knowledge of the possible effects of the virus on pregnancy and how changes in the pregnant woman influence the course of the disease can lead to appropriate interventions for the correct management of suspected patients. The article reviews data published in the literature with the aim of identifying possible perinatal and obstetric complications due to SARS-CoV-2 infection, observing vertical transmission, and analyzing the impact of pregnancy on the clinical course of COVID-19. Anatomical and physiological changes in pregnant women, such as the elevation of the diaphragm and immunosuppression, make them more susceptible to infection. On the other hand, immunosuppression can be considered a positive factor in minimizing the worsening of the multisystem inflammatory syndrome associated with the "cytokine storm". Obesity, cardiovascular disease and diabetes increased the risk of disease severity in pregnant women. The main consequence observed for the newborn was prematurity. Evidence has shown the possibility of vertical transmission and also passive immunization of the foetus. Immunizing pregnant women with the vaccines currently on offer seems to be the main protective measure for mother and fetus.

Keywords: *Pregnancy; premature birth; vertical transmission; SARS-CoV-2.*

1 INTRODUCTION

In December 2019, the first case of COVID-19 was confirmed in Wuhan, China. From that moment on, the virus began to spread across China and then around the world, becoming a pandemic. COVID-19 is caused by a new variant of the

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coronavirus, SARS-CoV-2 (Dana *et al.,* 2020). The disease is characterized as a respiratory syndrome, in which the main symptoms are cough and fever. Less frequent symptoms are dyspnea and fatigue (Muhidin et al., 2020). However, a growing body of evidence has shown the systemic effects of COVID-19, affecting multiple organs and systems, including damage to the central nervous system (Carvalho *et al*., 2020; Claudiano *et al*., 2021; Shantha *et al*., 2021; Arjmand *et al*., 2021; Yao *et al*., 2021; Yang *et al*., 2021).

The receptor binding domain (RBD) of the *spike* protein present in the viral capsid enables SARS-CoV-2 to bind to the angiotensin-converting enzyme 2 (ACE2) present on the surface of human cells. ACE2 is present in several cells, thus enabling the virus to enter and be present in different systems (Barrero-Castillero *et al.,* 2020). The multisystem inflammatory syndrome in COVID-19 is associated with the production of high levels of inflammatory cytokines, characterized as a “cytokine storm” (Carrijo-Carvalho *et al*, 2020).

Infection with the new coronavirus in pregnant women has raised concerns about the worsening of the disease in women due to the greater vulnerability inherent in pregnancy and the increased risk to the pregnant woman and the developing fetus as a result of the infection. This article presents data from a narrative review on COVID-19 in pregnancy, considering aspects of clinical management, vertical transmission, teratogenesis and prematurity. The search for articles published during the period of the pandemic, between 2020 and 2021, was carried out in the Pubmed and Google Scholar databases, using the terms “COVID-19”, “pregnancy”, “prematurity”, “management” and vertical transmission” in Portuguese and English.

From the results, we considered the most relevant articles that converged with the clinical manifestations in pregnant women and newborns with the new coronavirus, referring to placental dysfunctions and the possibility of COVID-19 vaccination in pregnant women. The exclusion criteria were opinion articles, guidelines and articles pertaining only to other types of virus. The data obtained was organized and presented together with a theoretical framework in order to reflect the analysis of how pregnancy makes women more susceptible to COVID-19 and how this disease, in turn, can affect pregnancy.

2 PHYSIOLOGICAL FACTORS THAT INCREASE THE SUSCEPTIBILITY OF PREGNANT WOMEN TO COVID-19

In the midst of the COVID-19 pandemic, a portion of the population has been at greater risk of infection, including pregnant and puerperal women, considering that pregnancy is a period vulnerable to infectious diseases, especially respiratory infections, with a greater risk of perinatal and obstetric complications, caused, in particular, by anatomophysiological changes and the immune response (Yee *et al*., 2020).

Throughout pregnancy, pregnant women undergo anatomical changes in the thorax and an elevation in the resting position of the diaphragm, thus causing a decrease in lung capacity (Pinto *et al*., 2015). Lung expansion is also reduced, as the organs of the respiratory system tend to increase in size, and this swelling is caused by increased levels of oestrogen and progesterone. These women are therefore more vulnerable to contracting respiratory pathogens and developing serious respiratory problems (Figure 1). In addition, the gestational period is a state of hypercoagulation. Therefore, pregnant women with SARS-CoV-2 may have a higher risk of thrombosis (Liu *et al*., 2020; Wastnedge *et al*., 2021).

Pregnancy is a period when a woman's immune system resistance is low (Figure 1). This is because maternal immunity must be altered to tolerate certain fetal antigens by suppressing cell-mediated immunity (Yee *et.al.,* 2020). Due to the suppression of adaptive immune response mechanisms during pregnancy, there is a decrease in the number of B and T lymphocytes (Liu *et al*., 2020). As a result of the alteration in cellular immunity, pregnant women are more susceptible to intracellular pathogens such as viruses and bacteria, and are more likely to have a worse prognosis (Alzamora *et.al.,* 2020). The third trimester of pregnancy is a pro-inflammatory period, contributing to more severe inflammatory conditions of the disease, characterized as a "cytokine storm" (Liu *et al*., 2020).

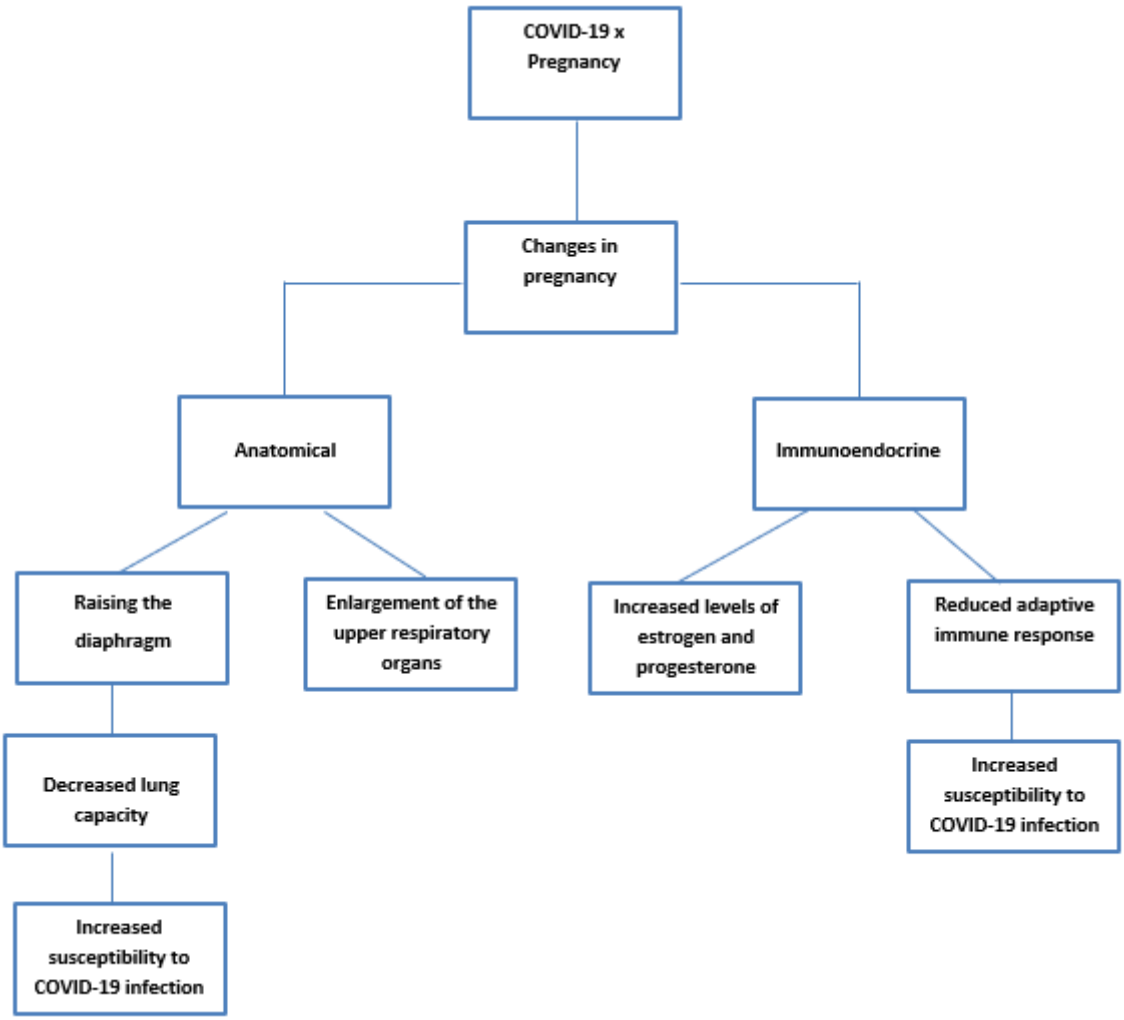

Figure 1. Physiological changes in pregnancy and possible relationships with COVID-19.
Source: Authors.

The third trimester is the period of pregnancy when women are most at risk of serious consequences of COVID-19, with the need for ICU admission and the use of mechanical ventilation (Yee *et.al*., 2020; Elizandro *et al*., 2021; Almeida *et al*., 2021; Dalfert, 2022). A study in Brazil evaluated pregnant women with severe acute respiratory syndrome who tested positive for COVID-19 and showed that they had a high rate of hospitalization and death, and the predominant comorbidity was heart disease (Godoi *et al*., 2021). Other Brazilian studies have pointed to the presence of comorbidity as a risk factor for more severe disease outcomes (Brito *et al*, 2021; Elizandro *et al*., 2021). Dalfert (2022) observed thatpregnant women who underwent the prone position in the ICU had an average body mass index of 33.14 (± 4.56) and an average SAPS III of 52.71 (± 10.09), 43% of whom were diagnosed with diabetes mellitus and 29% with systemic arterial hypertension. Another study showed that,

among hospitalized pregnant women who died, 74% had at least one associated comorbidity, such as chronic cardiovascular disease, diabetes, obesity, hypertension and asthma (Almeida *et al*, 2021).

On the other hand, a meta-analysis revealed that pregnant women infected with COVID-19 manifested milder symptoms with a lower prevalence of fatigue, cough and fever when compared to the general population. However, it is debated whether sociodemographic characteristics favor this difference, since pregnant women are younger than the general population and have a lower prevalence of comorbidities (Yee *et al.*, 2020). The same analysis showed a greater tendency for leukocytosis in pregnant women compared to the general population, and a lower increase in C-reactive protein, possibly due to the changes in the immune response that occur during pregnancy.

The COVID-19 rate in pregnant women varied geographically, related to the prevalence of the virus in the population. In a study in New York City, for example, 20% of 161 pregnant women tested positive for SARS-CoV-2, 13% of whom were asymptomatic. By contrast, in Connecticut it was found that 3.9% of pregnant women tested positive for the virus, with 2.9% asymptomatic (Barrero- Castillero *et al*., 2020). In Brazil, an epidemiological study by Almeida et al. (2021) evaluated 5,182 pregnant and postpartum women admitted to various hospitals who tested positive for COVID-19. The majority (65%) of pregnant women hospitalized for COVID-19 were in the third trimester of pregnancy. There was a death rate of 14.8% among puerperal women and 5.6% among pregnant women, 4.0% in the first trimester, 7.9% in the second trimester and 5.3% in the third trimester. The use of steroids in women who have been infected with COVID-19 has led to a more severe course of the disease (Dana *et al*, 2020).

3 VERTICAL TRANSMISSION OF COVID-19

For the COVID-19 virus to establish infection, it needs receptors present in the human body, these receptors being angiotensin-converting enzyme 2 (ACE 2) and transmembrane serine protease 2. These two SARS-CoV-2 receptors should be found in a significant amount in specific cells present in the gestational period, at the maternal-fetal interface. In other words, it can be understood that because these receptors are present in certain cells in the gestational period, in greater quantity,

they make vertical transmission prone to occur (Fenizia *et al*., 2020). Thus, a possible risk of vertical transmission is considered, since the ACE2 receptor is expressed in the placenta (Dashraath *et al.,* 2020).

Although there is still no established rate for vertical transmission, some studies suggest that the transmission rate is small. Among 338 newborns, 5 were found to be positive for COVID-19, indicating vertical transmission of SARS-CoV-2 (Yee *et.al.,* 2020). Another analysis showed that only 1.9% of babies born to SARS-CoV-2 positive women tested positive for COVID-19 (Heath *et al*., 2020).

One study evaluated the presence of IgG and IgM antibodies in five neonates who tested positive for SARS-Cov-2. It is known that IgG can be transferred from the mother to the fetus through the placenta, but it is assumed that IgM cannot cross the placenta because it is larger. IgM was observed in one of the newborns, indicating possible presentation to the virus prior to birth due to vertical transmission (Yee *et.al.,* 2020). On the other hand, IgG and IgM antibodies were also found in serum samples from newborns of pregnant women infected with COVID-19, although SARS-CoV-2 was not identified by the PCR test (Yee *et al*., 2020). These findings do not rule out the possibility of the development of active immunity in the fetus through contact with viral antigens during pregnancy, or even through subclinical infections that are not laboratory positive, since the PCR test has a very short evaluation window, making it possible to detect the virus only a few days after infection or the onset of symptoms.

Another important aspect of vertical transmission is the low probability of infection during a caesarean section. However, normal childbirth is not contraindicated either (Alzamora *et al.,* 2020). Furthermore, it is important to note that, in addition to the transplacental route, perinatal transmission of COVID-19 can also occur after delivery through contact between the neonate and droplets containing viral particles (Barrero-Castillero *et al.,* 2020).

4 CONSEQUENCES OF COVID-19 FOR PREGNANT WOMEN AND NEWBORNS

There is a possibility that infected newborns will show no symptoms, while others who are considered symptomatic may show fever, food intolerance and respiratory discomfort. Other primary symptoms reported in neonates were shortness of breath, elevated heart rate, as well as vomiting and skin rashes after the birth of positive mothers. However, none of these newborns tested positive for SARS-CoV-2,

and tests on amniotic fluid, cord blood and breast milk from infected mothers were negative (Liu *et al*, 2020).

Laboratory findings have shown, in infected neonates, elevated counts in the number of leukocytes, creatine phosphokinase, C-reactive protein and/or procalcitonin, and liver enzymes (Barrero-Castillero *et al*., 2020). The case report of a baby, with proven transplacental transmission, reported neurological findings, comprising white matter damage on brain MRI, irritability and the presence of inflammation in the cerebrospinal fluid (Barrero-Castillero *et al*., 2020). Even if it is not possible to detect COVID-19 infection in the fetus during pregnancy, greater attention is recommended for the children of positive pregnant women, for possible risks of presenting attention deficit disorder, hyperactivity due to inflammation, and abnormalities that may be related to organ growth and other maternal changes in response to infection by the virus (Dana *et al*., 2020).

Management also involves taking care to prescribe drugs that have a low risk of teratogenicity and toxicity for the fetus, taking into account the risks inherent in each trimester of pregnancy. Pregnant women infected with the virus can progress to perinatal complications, such as fetal prematurity and neonatal death (Dana *et al*, 2020; Smith *et al.,* 2020).

Even with mild symptoms of the disease, there may be a need for emergency caesarean surgery. In some cases, women with the most severe symptoms resulted in premature birth, neonates weighing less than 2.5kg and gastrointestinal complications (Smith *et al.,* 2020). A 34-week premature birth was reported in which the pregnant woman was positive for SARS-COV-2 and the *swab* test on the newborn was also positive. (Fenizia *et.al*., 2020).

With the pandemic there was a small increase in cases of premature birth, suggesting that social isolation promotes an increase in general maternal inflammation and this inflammation together with other processes interfered with by immunity would lead to premature birth (Hedermann *et al*., 2020). Infection of pregnant women in the third trimester can be a risk factor for premature birth, fetal distress, and early rupture of membranes (MUHIDIN *et al*., 2020).

5 EFFECTS OF COVID-19 ON THE PLACENTA

COVID-19 infections in pregnancy may be associated with increased plasma

concentrations of interleukin alpha, IL-7, IL-10, granulocyte colony-stimulating factor and gamma interferon. In pregnant women, from the first to the third trimester, the cytokines induced by the virus cause a serious inflammatory state. Despite the villous syncytiotrophoblast, which covers the placental surface and provides a protective barrier to the placenta, viral infections can occur, as well as vertical transmission. Histopathological analysis of the placenta of women infected with the virus suggested hypoxia damage, with the symptom increasing mainly at the time of delivery, which could lead to fetal distress (Souza *et al.,* 2021). However, according to a case report where a histopathological analysis of the placenta was carried out, it was noted that acute chronic intervillous inflammation was present and that the RT-PCR reaction on the placental tissue was positive for SARS-CoV-2 (Barrero-Castillero *et al.,* 2020).

6 CLINICAL MANAGEMENT OF COVID-19 IN PREGNANCY AND THE PUERPERIUM

The test considered the gold standard for diagnosing COVID-19 infection is RT-PCR, carried out on samples taken by *swab,* nasal and nasopharyngeal (Barrero-Castillero *et al.,* 2020).

Clinical management after SARS-CoV-2 infection in newborns is mainly supportive, thus encompassing respiratory support, fluid and electrolyte therapy, oxygen use, and the use of antibiotics in cases of suspected bacterial co-infection (Barrero-Castillero *et al.,* 2020).

At the beginning of the COVID-19 pandemic, the separation of mother and newborn was chosen as a prevention measure, but the likelihood of perinatal and postnatal transmission is not known (Barrero-Castillero *et al.,* 2020). Although the US Centers for Disease Control and Prevention initially proposed the temporary separation of positive or suspected pregnant women from their newborns, with rooms separated by a distance of at least 6 feet, the American Academy of Family Physicians demonstrated that the risk of infection for newborns separated from their mothers compared to those who maintained contact would be the same (Barrero-Castillero *et al.,* 2020). Separation between mother and child can lead to a reduction in the emotional bond between the two, as well as impairing breastfeeding. Thus, it was later recommended that mothers with COVID-19 should be encouraged to

breastfeed, adopting protective measures such as wearing a mask (Wastnedge *et al*, 2021).

7 VACCINATING PREGNANT AND POSTPARTUM WOMEN

Considering the seriousness of the pandemic, the emergency production of vaccines was necessary. However, it is important to evaluate the effectiveness of vaccines, their application and the vaccination schedule during pregnancy. Considering the anatomical and physiological changes that occur in a woman's body during pregnancy, as well as changes in immune responses, vaccination reactions may differ from those observed in the non-pregnant population (Heath *et al.*, 2020; Beigi *et al.,* 2021).

During the pandemic, some people showed vaccine hesitancy, which became even worse during pregnancy. The main doubts and questions regarding vaccination were whether the antibodies that recognize the *spike* protein of SARS-CoV-2 could cross-react with the protein found in the placenta, syncytin 1, and thus cause damage to the placenta (Male, 2021). The process of immunizing the population began, using a regressive hierarchy of age, prioritizing, in addition to the elderly, people with comorbidities, given their greater susceptibility to the virus.

At first, pregnant women were not included in the clinical trials, due to the lack of knowledge about possible reactions to the vaccine in the body. However, after conducting studies on vaccination in pregnant women and considering the benefits and risks, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention authorized vaccination in pregnant women in the United States (Burd *et al.*, 2021), a practice followed by other countries such as Brazil.

Studies have suggested that the messenger RNA fragment present in the vaccine is unable to cross the placenta because it is digested by the muscle cells in the area where the vaccine was administered. In contrast, the IgG produced in the mother after vaccination is able to cross the placenta and be transferred to the fetus, becoming an anti-SARS-CoV-2 antibody in the newborn's blood around 14 days after the first dose of the vaccine. Thus, this immunoglobulin promotes protection against the virus for the neonate in the first months of life (Burd *et al.*, 2021).

8 CONCLUSION

Pregnant women may be more susceptible to COVID-19, especially in the third trimester of pregnancy, due to the anatomophysiological, pro-inflammatory changes and possible risk of premature birth. The presence of comorbidities such as obesity, cardiovascular disease and diabetes mellitus increases the risk of the disease becoming severe in pregnant women. Vertical transmission can occur, although not at a high frequency, as well as complications for the neonate. Noteworthy is the passive immunization of the fetus through the transfer of antibodies from the pregnant woman to the fetus via the placenta.

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