

COVID 19 IN PREGNANCY: CLINICAL MANIFESTATIONS, MAIN COMPLICATIONS AND OBSTETRIC OUTCOMES

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Abstract: Introduction: Covid-19 is a disease that became popularly known in the year 2020, its etiological agent being Sars-Cov-2, a positive RNA virus from the coronavirus family, causing infections in the respiratory tract. Easy to spread, Covid soon spread around the world and, on March 11, 2020, the World Health Organization decreed the state of a pandemic. Clinical manifestations can range from asymptomatic to severe pneumonia, requiring admission to intensive care units and ventilatory support. Pregnancy is a condition that involves several physiological changes in the woman's body, requiring monitoring by health services for a good outcome for the maternal-fetal binomial. Pregnant women fall into the risk group for Covid-19 and require attention when infected by the Sars-Cov-2 virus. **Objectives:** Discuss the clinical manifestations, main complications and obstetric outcomes in pregnant women with Covid-19. **Methods:** The study consists of an integrative review of the existing literature through Google Scholar, Scielo and PubMed databases. **Discussion:** The main clinical manifestations observed in pregnant women infected with Sars-Cov-2 were fever and cough, and may also present dyspnea, diarrhea and anosmia in smaller proportions. With regard to obstetric complications, the ones that stood out the most were the PE LIKE syndrome, which simulates preeclampsia, the main gestational hypertensive disease, and the higher incidence of preterm births. The number of cesarean sections increased in pregnant women infected with the new coronavirus when compared to pregnancies without a diagnosis of Covid-19. **Conclusion:** The analyzed articles demonstrate that Covid-19 is related to the increase in the number of obstetric complications, mainly in the severe forms of the disease. Faced with this scenario, a rapid diagnosis is of paramount importance so that the demand for health

services is encouraged and both the mother and the baby do not suffer any type of sequel.

Keywords: "Covid-19" "Pregnancy"

INTRODUCTION

Coronaviruses (Cov) are positive RNA viruses, measuring about 60nm to 140nm in diameter, which have projections on their surface, giving this group a crown appearance (corona, in Latin) when observed microscopically. The ability of VOCs to cause respiratory infections in humans has been known since the 1960s, and they are the second leading cause of colds, second only to rhinoviruses.^{1,7,10}

The coronavirus became popularly known between 2002 and 2003, when it was described as the etiological agent of severe acute respiratory syndrome in humans, SARS. During this period, it was responsible for causing serious infections in the lower respiratory system, which could lead to fever and respiratory failure. However, it was quickly controlled and reached only a few countries such as the USA, China and Canada.^{1,5,10}

Covid-19 is an infectious disease that had its first cases reported on December 31, 2019 in the city of Wuhan, located in China. The etiological agent of this disease is Sars-Cov2, an RNA virus of the coronavirus family. Although this strain is less lethal than others in the family, it is known for its greater potential for dissemination. Contact through hand touch, hugs, or by droplets released into the air by coughing or sneezing, between a healthy person and a person contaminated by Sars-Cov-2, causes the infection to occur more frequently.^{1,2,8}

Today, Covid-19 already affects virtually all countries on five continents and is responsible for the great pandemic of the 21st century, recognized by the WHO on March 11, 2020.¹

The symptoms of Covid-19 are relative and patients can range from asymptomatic and

mildly symptomatic to cases of pneumonia and severe acute respiratory failure, requiring admission to an intensive care unit and mechanical ventilation.^{2,5} Studies indicate that people with chronic comorbidities (such as diabetes mellitus and high blood pressure) tend to experience the severe form of the disease, in addition to having higher mortality rates when compared to people without these conditions. Elderly and immunosuppressed people, due to lower rates of TCD4 cells, like people with comorbidities, are more likely to develop into a more severe condition of the disease. This public is classified as a risk group for Covid-19.^{3,5}

Some hypotheses have already been raised to try to clarify the mechanisms that influence the lethality caused by Sars-Cov2 in the human body. Studies suggest that this RNA virus enters cells through the binding of glycoprotein S present in its structure to the ACE2 receptor, which are receptors linked to the renin-angiotensin system, highly expressed in cells of the respiratory, cardiac and vascular systems. The entry of the virus into these cells leads to consequences such as damage to the cells of the bronchial tree, myocardial cells and risks of coagulation disorders, since they increase the inflammatory response of the human body leading to increased production of cytokines and tumor necrosis factors, in addition to the greater procoagulant stimulus.^{5,6,7}

To date, there are no scientifically proven drugs to treat Covid-19. Therefore, an early diagnosis is of paramount importance for patients with the Sars-Cov-2 virus to perform isolation and prevent further infections from occurring. Today, the gold standard for proving an infection with the new coronavirus is through RT-qPCR, a test that has high specificity despite the high rate of false negatives. In addition, chest CT is also recommended to complement the diagnosis,

being essential in assessing the severity of the infection.²²

Pregnancy is a period in which the mother's body undergoes several physiological changes, such as reduced lung volume due to increased diaphragmatic pressure, increased oxygen consumption, altered cellular immunity and a state of hypercoagulation. The pregnant woman has a greater need for oxygen, resulting in a 26% increase in respiratory rate to meet the demands of the fetus, in addition to presenting a 30-50% increase in cardiac output to supply the increased blood supply to organs such as the uterus, placenta and kidneys. Due to physiological changes, mainly in the respiratory and circulatory systems, the World Health Organization (WHO) classified pregnant women as a risk group in the pandemic context due to the increased probability of negative repercussions for the maternal-fetal binomial after an infection by Sars-Cov2, which has important repercussions on the cardiorespiratory system.^{3,9}

The main manifestations of pregnant women infected by the new coronavirus are fever and cough. Fatigue, myalgia, dyspnea, headache, diarrhea, nausea and vomiting are also described, but in smaller proportions. There is still not much information about vertical transmission in pregnant women infected with Sars-Cov2, but some maternal repercussions have already been described, such as an increased incidence of preeclampsia, premature rupture of ovular membranes (RPMO), hypertension and gestational diabetes.⁴

Neonatal complications such as asphyxia, low birth weight, pneumonia, perinatal death, rash and disseminated intravascular coagulation have also been reported. In addition, the growth in the number of cesarean sections and premature births due to maternal causes is a concern, since it contributes to the increase in neonatal morbidity and mortality.⁴

The present work is justified based on the importance of having a deeper knowledge about the repercussions caused by Sars-Cov-2 in the maternal organism, in order to avoid negative outcomes for the maternal-fetal binomial. It must also be noted that Covid-19 is a disease that has recently gained worldwide prominence and needs further studies to add to the literature on the subject.

OBJECTIVES

PRIMARY OBJECTIVES

1. Discuss the main clinical manifestations presented by the pregnant woman, as well as elucidate the most recurrent complications and what obstetric outcomes were observed.

METHODS

The study consists of an integrative review of existing literature through Google Scholar, Scielo and PubMed databases.

The descriptors were achieved by Medical Subject Headings (MESH) terms, being these: “*pregnancy*” “*covid-19*” “*pre-eclampsia*” “*prematurity*”. Such descriptors were used on the Pubmed website, using the Boolean operator “AND” in order to limit the search, with 134 publications being found.

For inclusion criteria, articles available in full text free of charge in Portuguese, English and Spanish and that discussed the main repercussions on the pregnant organism infected by the Sars-Cov-2 virus, published in the period from 2003 to 2021, were selected. exclusion, all articles that did not respond to the objective of the work and articles published before the year 2003 were discarded. Therefore, 23 articles of relevance to the study were selected.

DISCUSSION AND RESULTS

The signs and symptoms of Covid-19 caused by Sars-Cov-2 are variable. The main

symptoms experienced by individuals infected with the virus are dry cough, fever, myalgia and less frequently vomiting, dyspnea, diarrhea, hemoptysis, anosmia and ageusia. A systematic review of the literature carried out by Souza H et al. (2020) presented the main symptoms presented by pregnant women infected with the new coronavirus (**Table 1**).⁴

Signs and symptoms	Number of articles mentioned	Sample (%)
Cough	19 articles	592 pregnant women
Fever	21 articles	548 pregnant women
Diarrhea	13 articles	73 pregnant women
Dyspnoea	14 articles	226 pregnant women
Chest tightness	4 articles	8 pregnant women
Expectoration	4 articles	10 pregnant women
Myalgia or malaise	5 articles	20 pregnant women
Nausea or Vomiting	3 articles	3 pregnant women
Abdominal pain	4 articles	12 pregnant women
Headache	3 articles	8 pregnant women
Skin rash	2 articles	2 pregnant women
Anosmia	2 articles	175 pregnant women
Nasal congestion or runny nose	2 articles	2 pregnant women
Sore throat	2 articles	3 pregnant women
Dizziness	1 article	1 pregnant woman
Loss of appetite	1 article	2 pregnant women
Fatigue or discomfort	9 articles	45 pregnant women
Asymptomatic	8 articles	158 pregnant women

Table 1: Clinical status of pregnant women with Covid-19

Source: Table adapted from Souza H et al. (2020)⁴

Table 1 presents a systematic review of 23 studies carried out in 1,395 women who were infected by Sars-Cov-2 during pregnancy. The analysis of these articles showed that the most reported symptom was fever, present in 21 articles (91.3%), and cough, present in 19 articles (82.6%). The least cited symptoms are dizziness, sore throat, nasal congestion or runny nose, anosmia and rash.⁴

In the study carried out by Souza H et al. (2020), 42.43% of pregnant women infected with Sars-Cov-2 had a cough, while 39.38% of pregnant women had a fever. Dyspnea was cited in 16.2% of cases. Anosmia was observed in 12.5% of the pregnant women. 11.3% of patients were asymptomatic.⁴

Similarly, Allotey J et al. (2020) found in their work that the most prevalent manifestations in pregnant women were fever (40%) and cough (41%). It also states that pregnant and newly pregnant women are less likely to develop symptoms of Covid-19 when compared to non-pregnant women.²³

Accordingly, the study by Zaigham et al. (2020) analyzed 108 pregnant women with Covid-19. The main symptom reported was fever (68%), cough (34%), malaise (13%), dyspnea (12%) and diarrhea (6%).¹⁵

The work done by Elshafeey F et al. (2020) analyzed 33 studies with 385 pregnant women infected by Sars-Cov-2. 368 pregnant women (96.5%) had mild symptoms of the disease; 14 pregnant women (3.6%) had the severe form and 3 (0.8%) evolved to a critical condition.¹⁶

An observational study and meta-analysis performed by Di Mascio D et al. (2020) found that more than 90% of pregnant women infected with Sars-Cov-2 and with pneumonia had some complication during pregnancy. The ones that stood out the most were premature delivery, pre-eclampsia and cesarean section, in addition to neonatal death.²¹

Hypertensive diseases of pregnancy are the

most recurrent during the pregnancy period and are also the most responsible for maternal death when they are in the most severe form of the disease, such as eclampsia and HELLP syndrome. Pre-eclampsia (PE) is defined by the development of a hypertensive condition from the 20th week of gestation, with systolic pressure >140mmHg and/or diastolic >90mmHg, associated with proteinuria and/or edema of the hands and face. According to FEBRASGO, the worldwide incidence of PE is around 3 to 5%. Its etiology is still unknown, but it is known that the pathology is related to poor placental perfusion. The most accepted theories argue that genetic, environmental and immunological factors are involved in the genesis of pre-eclampsia. Studies suggest that the onset of placental hypoxia generates oxidative stress, with consequent activation and release of trophoblastic products and antiangiogenic factors. Due to inadequate trophoblastic invasion, the trophoblast produces toxic substances that lead to damage to the vascular endothelium and, consequently, to the clinical picture of preeclampsia. (**Figure 1**).^{11, 12, 13, 17}

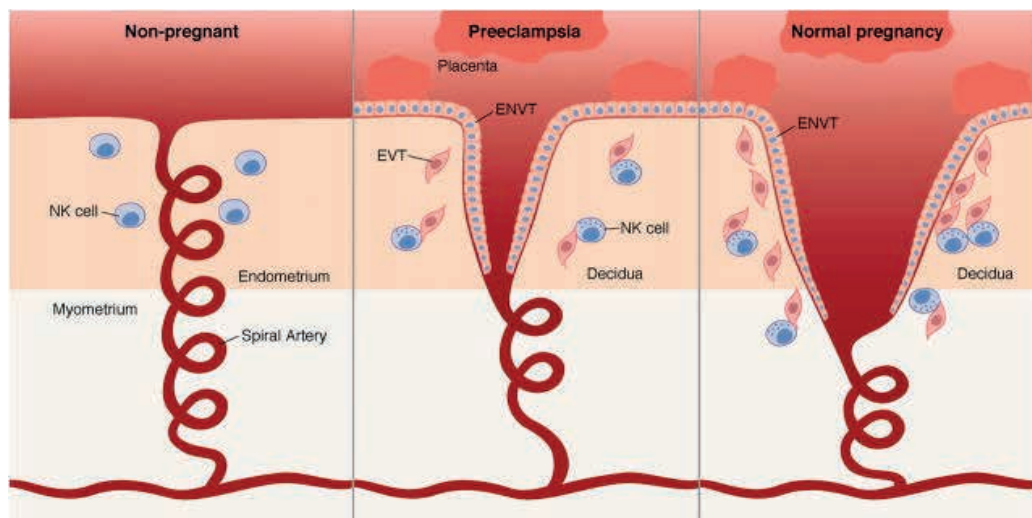


Figure 1

Source: Parham P (2004)¹⁷

In the face of the new coronavirus pandemic, the inflammatory syndrome caused by Covid-19 similar to preeclampsia, called PE LIKE syndrome, has been described. In addition to presenting the same signs and symptoms as pre-eclampsia, the PE LIKE syndrome shares a pathophysiological mechanism analogous to these hypertensive complications of pregnancy, which will be described below.^{11, 13}

As previously mentioned, the cellular invasion of Sars-Cov-2 is carried out through ACE2 receptors, related to the renin-angiotensin system. The angiotensin-converting enzyme 2 is highly expressed in the placenta, acting in the regulation of blood pressure in the pregnant organism. Infection with the new coronavirus provides an increase in angiotensin 2 rates in placental villi, resulting in vasoconstriction and poor placental perfusion, the mechanism by which preeclampsia is established. Concomitantly, pregnant women infected with Sars-Cov-2 and with PE have increased interleukin-6 (IL-6) and tumor necrosis factor (TNF-alpha), in addition to elevated serum ferritin.^{11, 13}

Differentiation of pre-eclampsia from PE

LIKE syndrome is made through biomarkers such as tyrosine kinase (sFlt-1), placental growth factor (PlGF), lactate dehydrogenase (LDH) and uterine artery pulsatility index (UtAPI), that undergo alterations in women with pre-eclampsia, remaining unchanged in pregnant women with PE LIKE syndrome. In addition, the resolution of the clinical picture can also be used to differentiate the two pathologies, since PE LIKE is treated concomitantly with the treatment of pneumonia caused by Sars-Cov-2 and pre-eclampsia is resolved through childbirth.¹¹

According to a study carried out by Mendoza M et al. (2020), about 65.2% of pregnant women infected with Sars-Cov-2 with signs of severity (pneumonia) showed signs and symptoms of PE. In patients whose severe form of Sars-Cov-2 did not manifest itself, the incidence was 0%, thus suggesting that the PE LIKE syndrome is related to the more advanced stages of Covid-19.¹²

Preterm birth is defined when it occurs before 37 weeks and after 20-22 weeks of gestation. According to FEBRASGO, premature births are related to 75% of morbidity and mortality among newborns, thus configuring a major

problem for obstetrics. Brazil, according to the WHO, is the 10th country with the most cases of prematurity in the world, reaching about 340,000 births per year. In the face of the coronavirus pandemic, there has been an increase in cases of premature births and cesarean sections in infected pregnant women registered by epidemiological surveillance.³

As mentioned above, several changes take place in the mother's body for pregnancy to occur. Some of these alterations are the decrease in the Th1-type immune response, so that the chances of rejection of the fetus in the uterus are reduced, the state of hypercoagulability due to the increase in coagulation factors VII, VIII, IX, X and XII, the reduction of levels of antiprothrombin III and protein S and increased levels of PAI-1 and PAI-2. These physiological changes of pregnancy related to the pathophysiology of Covid-19 (exacerbated inflammation, endothelial damage, increased oxidative stress and activation of the renin-angiotensin system) tend to occur with thromboembolic events that may predispose to severe acute events and preterm delivery.³

A study by Vielma S et al. (2020) showed that 16.9% of pregnant women diagnosed with Covid-19 and with mild symptoms experienced a premature birth. As for pregnant women with severe manifestations of the disease, all patients had preterm delivery.¹⁴

In the integrative literature review carried out by Souza H et al. (2020), 125 (18.52%) of the 675 pregnant women underwent premature labor, being considered cesarean sections or vaginal delivery.⁴

A study conducted in Türkiye by Oncel MY et al. (2020) found that among pregnant women infected with Sars-Cov-2, 71.2% of patients underwent cesarean section, 26.4% had premature delivery and 12.4% of neonates were born with low birth weight.²⁰

With regard to the mode of delivery chosen

for pregnant women infected with Sars-Cov-2, there is an increase in the number of cesarean sections when compared to pregnant women who did not test positive for Covid-19. A study by Prabhu M et al. (2020) analyzed 675 pregnant women, where 10.7% were diagnosed with the disease, and 78.6% were asymptomatic. Elective cesarean section was performed in 46.7% of symptomatic pregnant women, 45.5% of asymptomatic pregnant women and 30.9% of pregnant women not infected by the Sars-Cov-2 virus.¹⁸

Cao D et al. (2020) observed 10 pregnant women diagnosed with Covid-19 in Hubei, China. None of the pregnant women presented the severe form of the disease. 2 of the patients had vaginal delivery, while the other 8 underwent cesarean section, 6 elective and 2 intrapartum.¹⁹

In the systematic review carried out by Zaigham et al. (2020), 108 pregnant women were analyzed. 79 (92%) cesarean sections were reported, while 7 (8%) vaginal deliveries occurred, demonstrating a clear increase in the number of cesarean sections in women who were infected by Sars-Cov-2.¹⁵

The clinical outcome of pregnant women was analyzed in the study carried out by Souza H et al. (2020), which concluded that 11.68% of pregnant women required ventilatory support, 1.86% were admitted to the Intensive Care Unit and 0.43% of patients died.⁴

An analysis carried out by Souza A and Amorim M identified 9,609 pregnant and postpartum women in Brazil with severe acute respiratory syndrome between December 29, 2019 and August 31, 2020, the period that encompasses the beginning of the pandemic. 4,230 (44%) were diagnosed with Covid-19. 553 (5.7%) pregnant and puerperal women out of the 9,609 died, 354 (64%) of them as a result of infection with Sars-Cov-2. An increased mortality rate (8.4%) was observed when severe acute respiratory syndrome was

due to Covid-19.²⁴

CONCLUSION

Covid-19 is a recent disease that is still being studied. Its manifestations and consequences are related to each individual, making it difficult to specify exactly what the outcomes are for each patient. Due to the fact that there is still no specific treatment for those who have been infected by the new coronavirus, the indisputable importance of an early diagnosis is highlighted so that the patient's condition does not get worse.

It is important to take into consideration, that pregnancy is a unique moment in a woman's life, which in itself causes several physiological changes and can evolve with complications that put maternal and fetal life at risk.

In view of the analysis of the articles that were used for the present study, the main clinical manifestations that were inferred by the authors were fever and cough. Therefore, they are parameters that must be used to alert pregnant women about a possible infection of the new coronavirus. In the presence of these symptoms, the search for health care must be carried out so that the diagnosis is made early and a worsening of the condition is prevented.

Throughout the discussion of the present work, it is clear that Sars-Cov-2 has significant repercussions on the maternal organism, being responsible for the severity of the symptoms, leading to gestational hypertension (the PE LIKE syndrome) and mainly to premature births, which are directly related to increased maternal and neonatal mortality.

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