Jornal Memorial da Medicina 2020, vol. 2 (1), p.51-59

MEDICINA CLÍNICA

ISSN 2674-7103 (on-line) Review

Maternal-embryonic approach at Covid-19: implications for changes in the monitoring and management of pregnancy

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Abstract

The pathophysiology of Covid-19 has a cytokine storm, causing exacerbation of inflammatory lesions, mainly of the lungs and vascular endothelium. The mechanism of entry into the human cell uses the Angiotensin-Converting Enzyme 2 as a cell surface receptor. Among the most at-risk groups are pregnant women, due to the physiological, anatomical and immunological changes of the gestational cycle, causing susceptibility to infections. In addition, there are uncertainties about safe breastfeeding and possible vertical transmission. This group, which has a continuous obstetric follow-up, within pandemic circumstances, needed to minimize the risk of exposure in medical settings, using care through telehealth, as a helper. It was possible to replace some face-to-face visits to the clinic, when possible, by virtual ones, minimizing risks to exposure and providing a vehicle for direct communication with the doctor, which, in a way, offers pregnant women more peace of mind, essential to avoid possible complications by psychological stress that can generate inflammatory responses for mother and fetus, causing possible neuropsychiatric consequences. The objective of this narrative review study was to present an update of the data on the disease, as well as a change in management of the pregnant population. Despite being of great importance, virtual assistance does not replace face-to-face, and to get the most out of this new approach, there is a set of guidelines that can help health professionals. It is also important to warn of: changes in hospital management; reconciling ultrasound consultations with medical appointments, reducing the number of pregnant women leavings; telephone tracking of patients' symptoms before face-to-face attendance; and testing recommendations for covid-19, before entering hospitals.

Keywords: Covid-19; Pregnancy; Covid-19 physiology; Neonate-covid-19 relationship; Management.

Introduction

In the last two decades, there have been three epidemics of viral infectious disease caused by the Coronavirus family, being the main cause of human infections of the lower respiratory tract of that period. The Coronavirus family caused an outbreak with Sars-CoV in 2002, Acute Respiratory Syndrome and Middle East Respiratory Syndrome with Mers-CoV in 2012.[14,15] In December 2019, a new disease transmitted by the coronavirus, Covid-19, began to spread in Wuhan, China, is characterized by atypical pneumonia with acute lower respiratory tract infection that quickly spread to more than 160 countries, prompting the World Health Organization (WHO) to declare on January 30th, 2020, an international public health emergency and later a pandemic. [14-16]

Up to June 6th, 2020, Brazil already has 650,504 confirmed cases and 35,139 deaths by Covid-19, according to the Ministry of Health's epidemiological bulletin. Given these numbers, it is understood the severity of the disease and the importance of information about it, therefore, this article aims through a narrative review of the literature, to present an update of the data on the

disease, as well as the modification of management of pregnant population.[26]

The Role of Angiotensin-Converting Enzyme

It is believed that, upon the entry of the virus into the cell, Sars-CoV, and Sars-CoV-2, which cause Covid-19, use the same cell surface receptor, the Angiotensin-Converting Enzyme 2, which is a protein transmembrane present on the surface of different cells in the body, including the respiratory system. ACE 2 acts on the Renin-Angiotensin mechanism promoting vasodilation and assisting in the blood pressure regulation mechanism, so, once the virus uses it, there is a dysregulation in the expression of these receptors, by occupying its binding site or by destroying the invaded cell, causing exacerbation of Angiotensin II activation.[15,17]

The participation of ECA 2 also suggests that the organs with high expression of this are the main targets of infection by Covid-19. Among them are lungs, heart, kidneys, digestive tract, skin, adrenal glands, parathyroid glands, pituitary gland, pancreas and brain.[17]

An important pathophysiological mechanism of Covid-19 is related to a cytokine storm. This provides an exacerbation of inflammatory lesions, mainly in the lungs and vascular endothelial system, in addition to leading to apoptosis of T cells, causing a deficiency in the immune system.[14,15,17] Such a premise may be the beginning for elucidating the prognosis of patients in such different ways, relating the difference in the immune system response in each individual to the virus.[15]

Pregnant women as a risk group in Brazil

In April 2020, the Ministry of Health declared that pregnant women and puerperal women were part of the risk group for Covid-19 because, until then, only high-risk pregnant women were in the group. Although there are still no clear conclusions about the adverse effects of coronavirus on pregnant women, the inclusion was based on studies, as Schwartz[4] describes in his analysis, on already explained viruses, such as H1N1, Ebola virus, chickenpox, and hepatitis E, whose pathophysiology they can cause clinical severity and can be fatal in these groups when correlated to the clinical history of comorbidities. Thus, it is understood that the same physiological effects would also be caused by covid-19 infection.[4]

According to Schwartz[4], the great vulnerability of pregnant women during this pandemic period is due to physiological, anatomical and immunological changes in the gestation cycle, which can cause susceptibility to Covid-19 infection, as well as its severity. There are several changes, including: the suppression of cellular immunity; changes in the cardiovascular and respiratory system, involving increased oxygen consumption; changes in heart rate, and stroke volume, in addition to decreased lung capacity, among other changes.[4] Recently reported eight cases of mortality among pregnant women in Iran, none of them had a pre-existing condition of comorbidity to be above the risk of the general population.[1,2]

Although the severity of Sars-CoV-2 infection in the gestational period is understood, an analysis conducted at the Maternity and Child Health Hospital in Wuhan, China, the results were favorable to the good prognosis in pregnant women. When comparing non-pregnant women with pneumonia due to Covid-19, almost all infected pregnant women had mild or absent respiratory symptoms and none developed severe respiratory impairment or required intensive care.[3] In the same study, there was a high incidence of premature births in pregnant women with Covid-19, however, there is no relationship with complications resulting from severe maternal respiratory disease.

Reaffirming this study, another author reveals results with similar information indicating that pregnant women infected with Covid-19 have, for the most part, mild respiratory symptoms or are asymptomatic, with 90% of hospitalized pregnant women affected by Sars-CoV-2 infections. radiological signs suggestive of pneumonia, detected by x-ray or computed tomography, and the most common symptoms are fever, cough, and lymphopenia.[13] However, such outcomes should not underestimate the chances of developing the disease in its most severe form in pregnant women, causing a potential risk of life for the pregnant woman and the fetus.

An observed fact is that Covid-19 causes less serious adverse effects in pregnant women than the two preexisting coronavirus infections, the coronavirus related to Severe Acute Respiratory Syndrome (Sars) and the coronavirus related to the Middle East Respiratory Syndrome (MERS) .[5, 13]

Although the immune system in the gestation cycle is somewhat suppressed, a study of critical cases of Covid-19 was observed, in which pregnant women can modulate the system so that human chorionic gonadotropin (hCG) and progesterone can inhibit the pro-inflamatory pathway Th1, decreasing the tumor necrosis factor-α. Thus, it indicates that this modulation of the immune system protects pregnant women from Cytokine Storm syndrome and associated morbidity and mortality.[12]

Pregnant women infected with Sars-CoV-2.

To date, studies have shown that infection with Sars-CoV-2 can cause some adverse repercussions such as: premature birth (20.8%, 25/120), fetal distress (26.7%, 12/45), premature rupture of fetal membranes (13.0%, 10/77) and cesarean section (92.6%, 63/68). [10] The latter condition is led to occur by Covid-19 in pregnant women diagnosed with the infection, since the risk is uncertain of intrapartum transmission through vaginal delivery, as well as obstetric indications, including severe preeclampsia, history of cesarean sections and neonatal hypoxia[8, 13]

If it is proven that Covid-19 is an infection that has the capacity for intrauterine transmission, it can be classified in the Torch complex (toxoplasmosis, "other" infections, rubella, cytomegalovirus, and herpes simplex), that is, congenital infections acquired through mother to the fetus by the placenta. This means of contagion (except for the herpes simplex virus) is often due to the hematogenous route by which the virus circulates in the maternal bloodstream, enters the placenta, reaches the chorionic villous tree, fetal blood vessels and is transmitted to the fetus.[7]

Sars-CoV-2 has already been shown to produce RNAemia (presence of the RNA rotavirus), which further suggests the biological possibility of transplacental transmission through a hematogenous mother-fetus route.[11]

Studies comparing perinatal infections with other already pre-existing coronaviruses in animals have shown, for example, that murine coronavirus (M-CoV), a species of coronavirus that infects mice, can infect both the placenta and the fetus, as well as betaarterivirus suid 1, a porcine arterivirus related to the coronavirus.[11]

The results also showed that three babies tested positive for Covid-19, but two of them are assumed to have contracted from the mother because both developed the infection in the postpartum period and continued breastfeeding without wearing a mask. Another baby who was born vaginally and did not feed on the mother's milk, developed respiratory symptoms requiring a day of ventilation, but did not test positive.[5] Another study also demonstrated a newborn, born by cesarean delivery whose mother was diagnosed with pneumonia by Sars-CoV-2, which in his serology was positive for IgM. In this case, the child was born in a relative pressure isolation room, and his mother was wearing an N95 mask and had no direct contact with the baby. Based on this, it is suggested that vertical transmission occurred, although the test for nucleic acid indicated negative.[11]

In an analysis carried out by Schwartz[7], with 38 pregnant women from China diagnosed with Covid-19, 37 of which were confirmed by Sars-CoV-2 positive rt-PCR, there were no cases of severe pneumonia and maternal death and in all newborns, the results were negative for the new viral pathogen through samples obtained from the placenta, amniotic fluid, umbilical cord blood, gastric juice, and oropharyngeal swab. In the same study in question, some of the pregnant women presented comorbid conditions such as pre-eclampsia, pregnancy-induced hypertension, uterine scarring, gestational diabetes, and uterine atony. Thus, these comorbidities did not result in life-threatening maternal disease by Sars-CoV-2 and were not a risk factor for intrauterine transmission to the fetus.[7]

At the Hospital of Wuhan University in China, Chen and colleagues[8] conducted a study evaluating nine pregnant women diagnosed with Covid-19 pneumonia and later six of the nine newborns. None of the patients had underlying diseases such as diabetes, hypertension, or cardiovascular disease. The most common

symptoms for Sars-CoV-2 among pregnant women were fever before or after cesarean delivery and none developed severe pneumonia, requiring mechanical ventilation, or mortality from Covid-19 pneumonia.

Complications during pregnancy that emerged after infection by the virus under study included fetal distress and premature rupture of the membrane, however, in none of the newborns was the Sars-CoV-2 virus detected in the samples collected in the time of cesarean delivery, a period chosen because in this way the samples would not be contaminated and best represent the conditions of the intrauterine fetus.[8]

However, the study reiterates that non-fetal infection due to vertical intrauterine transmission may be affected by the small sample size and the stage of pregnancy at the beginning of Covid-19 infection. This is because all pregnant women in the survey were recruited in the third trimester, and therefore, it is not possible to determine the possibility of vertical intrauterine transmission during the first or the second trimester. An example of this reasoning is rubella infection, which in the first trimester can affect more than 50% of fetuses due to intrauterine infection, however, if it occurs by the end of the second trimester, the incidence rate is reduced by half.[8]

Although most reports claim that there is no vertical transmission of Covid-19 to the fetus, the emerging evidence from a neonate with high IgM antibodies to Sars-CoV-2 highlights the possibility of this phenomenon. [4,7,8] Mehan, Venkatesh and Girish[9] quoted Zeng et at. who has elaborated a report on newborns infected with Covid-19 who developed severe clinical sequelae. Many authors attribute these results to prematurity, asphyxia, and sepsis, however, they can be associated with the combination of the pathological contributions of the virus to prematurity and the potential vertical transmission, which can bring adverse results to the newborn.[9] The viral pathogen can also be found in fecal samples, suggesting that perianal colonization may progress to an intrapartum infection in the newborn during labor.[11, 13]

Therefore, it is noted the existence of many oppositions in the face of studies referring to vertical transmission of Covid-19, since the studies previously presented are equally opposed in numbers on the occurrence of mother-to-fetus transmission, pointing to the need for further studies.

Mechanism of action of Covid-19 in pregnant women

Recent studies have revealed the high expression of Sars-CoV-2 receptors, the transmembrane serine protease 2, TMPRSS2, and the angiotensin-converting enzyme 2, ACE 2, in cells of the maternal-fetal interface.[9] The virus invades cells linking it is linked to ACE 2 and modulates the expression of this protein in host cells, thus, Jing et al.[10], address the potential of the influence of ECA 2 on the physiology of pregnant women with covid-19, since the enzyme is widely expressed in the human placenta.

ACE 2 is present in the primary and secondary villi of the placenta, in the maternal stroma and the umbilical cord. Also, it is present throughout pregnancy, presenting its highest level at the beginning of the gestational cycle. Thus, the possibility of viral infection by the placenta is suggested.[10]

Besides, some studies show the presence of ECA 2 in female breasts. Jing et al[10] quoted Wu et al who has, observed that one of three samples of milk from the breast were positive for Sars-CoV-2 in a nucleic acid test, indicating the chance of transmission through breastfeeding.[10]

Normally, ACE 2 hydrolyzes angiotensin II to angiotensin-1-7 and angiotensin I to angiotensin-1-9, which will quickly be converted to angiotensin-1-7. This sequence controls the blood pressure and the hydro-salinity balance of pregnant women. Thus, the change in the expression of angiotensin II, ACE 2 and angiotensin-1-7 may be involved in hypertension of the pregnant woman, eclampsia, and pre-eclampsia. The latter condition may be related to the suppression of angiotensin-1-7 in the plasma and the high expression of angiotensin II in the placental villus during pre-eclampsia causes a decrease in blood flow and nutritional supply in the fetus. Meanwhile, the low level of ACE 2 and angiotensin-1-7 in the placenta is associated with intrauterine growth restriction, that is, there is a delay in the growth of the fetus.

Health Care of Sars-CoV-2 positive pregnant women

With the health measures that recommend social distance to avoid exposure to imminent risks for this population, the management of obstetric patients needed to be adapted. Worldwide, professionals in the field have resorted to various mechanisms for the continuation of care promoting biosafety safety, concomitant with the safety of pregnant women and babies, to avoid contagion. From this, two aspects need to be considered: (1) How to change the practice to minimize the viral exposure of patients and healthy health professionals; (2) How to use outpatient resources to minimize the hospital burden in caring for patients with covid-19. [18-20]

One of the aid mechanisms came with the approval by the Medical Council for the use of technologies such as virtual consultation, telehealth and/or telemedicine. This represents a great ally to reduce face-to-face interaction in prenatal consultations and consequently avoid an additional source of exposure to the virus.[18,21] It is also important to remember that virtual consultations can provide women with a feeling of decreased care, so a longer duration should be considered compared to face-to-face, in addition to explaining that face-to-face service will remain available for any complications.[18,22]

According to London et al.[22] first, the identification of patients with scheduled appointments for a tracking of symptoms and exposure to the virus must be done by telephone before their presentation at the office. When there is a positive detection of the questions, postponing the visit for 14 days and/or postponing it for at least eight days after the symptoms cease are indicated. Another issue is the decrease in the frequency of ultrasound exams.[18.22]

It is important the presence of a specific professional or until the gynecologist/obstetrician has a direct line to answer questions. It is necessary to understand the fears that this woman faces, which are linked to many doubts. The infrastructure of a reference provider that makes regular telephone consultations, with the appropriate frequency to the patient's demand, is fundamental. This will reduce the flow of low acuity in-hospital screening areas.[18.22]

During the pandemic, pregnant women should be encouraged to obtain a sphygmomanometer. Patients monitored for hypertension should receive written instructions for identifying important signs and symptoms, as well as facilitating contact with the professional who accompanies them to report any concerns about changing status.[19]

Among the Conditions that represent a high risk for pregnant women, the following stand out: [19,23,24]

- Hypertensive disorders of pregnancy including preeclampsia, gestational hypertension, and chronic hypertension;
- Diabetes mellitus pre-gestational and gestational;
- Maternal cardiovascular disease;
- Maternal neurological conditions;
- Bad obstetric history, including previous stillbirths, fetal conditions such as growth restriction intrauterine (IUGR), congenital anomalies and multiple pregnancies, including monochorionic placentation;

Blood pressure should be measured and recorded regularly by patients at home so that they can make a reliable report to the professional they accompany.[18] An automatic sphygmomanometer, which the patient feels safe with, is essential especially for patients with chronic hypertension or pregnancy, pre-eclampsia or risk factors for the development of hypertensive diseases in pregnancy that receives some type of care by telehealth.[19, 24]

Analyzing the recommendations of the Brazilian Federation of Gynecology and Obstetrics Associations [21], the World Health Organization and other studies, some feasible recommendations are listed for framing the pandemic scenario, being presented in Chart 1.

Table 1: Recommendations about the Telehealth scheme.

Recommendation for consultation	**Modality**	**Guidelines**
From conception/before the 11th week	Virtual	Obtaining clinical history, vitamin prescription, guidance on nutrition, weight gain, risk factors, morbidities, and the need for revised genetic screening.
11th-14th week	Presential	Prenatal physical examination and blood test. You should associate the visit with the first-trimester ultrasound (nuchal translucency). Chorionic villus sampling can be performed on this visit if desired. It is also advisable that in this first face-to-face consultation the patient has instructions for home blood pressure and glucose measurement for control.
15th-18th week, being at least 4 weeks after the previous consultation	Virtual	A review of the systems, including mental health in the face of the pandemic and assessment of intimate partner violence, should be undertaken. The requested laboratory exams are also reviewed. It is also recommended that the patient measure BP and body weight at home and report to her doctor.
19th-22nd week, being at least 4 weeks after the previous consultation	Presential	It is preferable to reconcile it with the ultrasound of the fetal anatomy. Clinical systems and parameters are revised as vital signs, including weight.
23rd-26th week	Virtual	Anamnesis for systems, counseling, and screening for diabetes and gestational hypertension. It is also recommended that the patient measure BP and body weight at home and report to her doctor.
27th - 28th week, being at least 4 weeks after the previous consultation	Presential	Physical examination with vital signs, anthropometric data including uterus fundus height. Period of blood tests in the third trimester, including screening for gestational diabetes mellitus, fetal heartbeat, and vaccines.
between 29 to 35 weeks, biweekly	Virtual	The systems are reviewed, education on breastfeeding, precautions for premature births and pre-eclampsia, and advice on the delivery specifications related to covid-19. It is also recommended that the patient measure BP and body weight at home and report it to her doctor.
36th to 40th From the 36th it is done weekly	Presential	The height of the fundus and the screening for the colonization of group B streptococcus, cardiac tones by Doppler, vital signs, and general anthropometric measurements were again performed. Advice and questions from the patient. Physical examination with vital signs.

Source: Telehealth for high-risk pregnancies in the scenario of the covid-19 pandemic. [18]; A Proposed Plan for Prenatal Care to Minimize Risks of COVID-19 to Patients and Providers.[19]; World Health Organization; Protocol for

the clinical management of Coronavirus in primary health care [20]; Brazilian Federation of Gynecology and Obstetrics Associations[21].

The format of prenatal care should be guided by the clinical specifications and the patient's social and physiological circumstances. It requires format adaptation, mainly, patients that belong to high-risk classification.[19] This information is for guidance only, and there is no requirement to strictly follow it, it only shows possibilities in which prenatal care can be adapted.[21]

It is important the presence of a trained professional, who this patient reports for the correct use of this equipment, including that a measurement supervised by the doctor is made in the online consultations so that he can identify possible errors in handling.[19] How hypertension in pregnancy can worsen at the end of the third trimester, patients must present in person after 36 weeks of gestation.[24]

For pregnant women with pre-gestational and gestational diabetes, attention should be paid to education in self-management of the disease and even if this woman has home access to glucose meters so that she can make careful monitoring, recording all measurements in an organized way so that this report is correctly forwarded to your doctor, to be agreed.[19]

If the patient receives a prescription for insulin, she should be properly advised to administer it in a consultation that can be virtual or in person. E-mail or telephone communication is used weekly to review blood glucose measurements. The same can be done for patients with hypertensive disorders of pregnancy.[18]

Strategies for welcoming hospitalized pregnant women

It is of great importance that all patients referred for screening or scheduled for cesarean section be screened, at least for symptoms related to Covid-19 before the presentation.[19,22] Ideally, hospitals should provide examinations at the entrance, including for visitors who accompany patients.

The waiting room may need to be readjusted, removing most chairs to prevent large groups from congregating or creating a closed space for patient entry.[22] It is advisable that the availability of specific recovery rooms for diagnosed patients, which may be one elective operating room that is not being used, for example, or another adaptable location.[19]

One of the biggest challenges faced in Brazil is still the scarcity of the laboratory test for Covid-19 and/or the long waiting time for the result, which limits the ability to organize and protect patients. So, if identified as possible, it should it is strongly advised that pregnant patients take a test near the end of pregnancy, thereby limiting exposure.[22]

Strict screening of companions should be part of the protocol, including mandatory temperature measurement for all and allowing only one during the entire hospitalization. The technology can also help support systems during hospitalizations, such as virtual doulas, telephone and video connections, whose potential is significant to relieve the patient's anxiety.[22]

After the baby is born, in Brazil, the Ministry of Health and the Brazilian Federation of Gynecology and Obstetrics Associations follow the recommendations of the World Health Organization to continue breastfeeding, since there is insufficient scientific evidence to confirm transmission through this and considering the benefits of this food for the infant, however, the recommendation is made with some safety caveats for the mother who tests positive for the virus or even the mother who does not feel safe enough for such an act, given the uncertainties of the pandemic, among these recommendations being the possibility of expressing milk and offering it by a third party who is sure that the disease is absent, thus avoiding direct contact by the mother and possible contamination of the baby.[25]

The WHO also advises an appropriate hand washing that lasts at least twenty seconds before touching the baby, wearing a mask so that it completely covers the nose and mouth during breastfeeding, pay attention to the rigor for cleaning the breast pumps. In addition, it is recommended the constant use of the facial mask by third parties when in contact with this newborn, since children due to the risk of suffocation cannot use it.[25]

Effects of the pandemic on maternal and child health

It is a priority in the assistance to guarantee the well-being of the pregnant woman during this pandemic period to be given greater psychological support, due to exposure to situations that can trigger high levels of stress, anxiety, or symptoms of depression. This may represent a risk factor for disorders in the neuronal development of children and adults, both attention deficit hyperactivity/impulsivity disorder (TDH), autistic spectrum disorder (ASD), schizophrenic spectrum disorder, antisocial behavior, and depressive symptoms. In this perspective, a possible justification for causing these complications would be the increase in maternal inflammation and changes in the hypothalamic-pituitary-adrenal axis, related to hormones. [6]

Abdoli et al.[6], details the subject by comparing the impact of prenatal stress on the pregnant woman and the child when: a) the mother is exposed to stressful life events; b) the mother is exposed to chronic stress. In the first case, high levels of interleukins in umbilical cord blood and elevated tumor necrosis factor-α were observed, whereas in continuous stress, in addition to high interleukins, the study shows an increase in C-reactive protein, inflammation of the placenta in addition to impaired immune coordination of the impaired hypothalamic-pituitary-adrenal axis.[6]

Conclusion

Although there is still no proven evidence about the adverse effects that Covid-19 causes in pregnant women, evidence demonstrates that both the physiological change in pregnancy itself and some clinical correlations in which the virus can interfere, harm the health of the pregnant woman in a way that can be fatal.

A possible increase in the rates of premature births is observed, although the neonatal outcomes were mostly positive. There are no data to assess the risk of congenital malformations or outcomes associated with the first trimester of pregnancy.

It is difficult to state the impact that coronavirus infection can result on the embryo and fetus, as it is a condition that will be closely related to factors such as the agent, time of gestational infection, and the interaction between the maternal and embryonic organisms.

Also, there is a clear need for further investigation into the possibility of vertical transmission, since there are still significant differences in the subject. In addition, it is emerging that public policies ahead of the management of the health system seek, based on scientific evidence, to ensure increasingly efficient management for the well-being of pregnant women and newborns.

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Received: June 23, 2020 Accepted: July 1, 2020