Review

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Review

SARS CoV2 Infection and Preeclampsia. How an Infection Can Help Us to Know More about an Obstetric Condition

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Abstract: In this review, we aimed to understand the relationship between SARS-CoV-2 infection and preeclampsia severity in infected pregnant women. Pregnant women with SARS- CoV-2 infection have been shown to have a significantly increased risk of maternal death, ICU admission, preterm delivery, and stillbirth compared with those without infection. The risk of preeclampsia also increases in pregnant women infected with SARS-CoV-2, particularly in those with severe symptoms. We emphasize the importance of specialized clinical management to prevent poor pregnancy outcomes in this situation. The association between COVID-19 and preeclampsia (PE) is likely due to multiple mechanisms, including the direct effects of the virus on trophoblast function and the arterial wall, acute atherosis, local inflammation leading to placental ischemia, exaggerated inflammatory responses in pregnant women, SARS-CoV-2-related myocardial injury, cytokine storm, and thrombotic microangiopathy. Emphasis has been placed on the potential impact of COVID-19 on pregnant women, specifically in relation to thrombotic complications, placental dysfunction, and cardiovascular dysfunction. Undoubtedly, one of the diagnostic tools to differentiate between COVID-19-induced preeclampsia-like syndrome and true preeclampsia is the use of biomarkers, such as the sFlt-1/PlGF ratio. We wish to highlight the potential for COVID-19-induced myocardial injury in pregnant women and the associated increase in maternal mortality rate. Vaccination against COVID-19 in the general population and in pregnant women in particular, drastically reduced the severity of the disease. There is an urgent need to continue the follow-up of these women and their children to detect the appearance of sequelae of the disease or peristent COVID 19 .

Keywords: SARS- Cov-2; COVID 19; Preclampsia; pregnancy; hypertensive disorders of pregnancy; inflammation; cytokines; thrombotic

Introduction

The World Health Organization (WHO) officially declared the outbreak of severe acute respiratory syndrome (SARS) caused by coronavirus 2 (CoV-2) a pandemic on March 11, 2020. (1) Since then, several studies have been published on the evolution of the disease from its beginning, the differences according to the variety of the virus, and the transformation into a mild respiratory disease after population vaccination.

The updated data reports that until August 2022, there have been more than 548 million cases diagnosed around the world , there have been more than 6 million deaths from COVID 19 disease and about 69% of the population have received at least one dose of the vaccine, more than 1.6 billion doses of vaccine have been administered.(2)

Coronavirus disease 2019 (COVID -19) usually presents with fever, dry cough, and fatigue; however, up to 14% of cases can progress to severe pneumonia and 5% to severe acute respiratory syndrome (SARS), both of which require admission to intensive care for concentrated respiratory

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support. (3) Although COVID -19 is primarily a respiratory infection, has important systemic effects including hypertension, kidney disease, thrombocytopenia and liver injury.(3)

Numerous studies have been published that sought to identify the effects of SARS CoV -2 infection in pregnant women for various reasons: it seemed to be a population with greater susceptibility; there have been no studies on the effects of other coronaviruses on the fetus in previous pandemics and because it was necessary to guide doctors and pregnant women about the consequences of viral infection on the health of the fetus and mother. (4,5)

During pregnancy, several respiratory viral infections increase the risk of adverse obstetric and neonatal outcomes. (6) Physiological and immunological variations that occur during a normal pregnancy can cause systemic effects that increase the risk of complications due to respiratory infections. Changes in maternal cardiovascular and respiratory systems, such as increased heart rate and oxygen consumption, increased stroke volume, decreased lung capacity, and immune adaptation to allow the fetus to tolerate different antigenic characteristics, all of which increase the risk of developing severe respiratory diseases in pregnant women. The results of multiple influenza studies have demonstrated an increased risk of maternal morbidity and mortality compared to non-pregnant women.(7) This association was also previously demonstrated when pregnant women developed any of two pathogenic coronavirus infections: severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). (8)

How COVID 19 and preeclampsia

In addition to the respiratory symptoms of COVID -19, systemic effects were gradually defined and differentiated, and some authors observed that SARS CoV 2 infection during pregnancy could be associated with an increase relative risk (RR) of PE and other complications of pregnancy. (9, 10,11,12,13)

Almost all published studies concluded that infected pregnant women presented a worse evolution/severity of the disease when compared to their non-pregnant partners, particularly when the infection occurred in the 3rd trimester.(14) Pregnancy was included as a comorbidity in the CDC classification of risk factors for severe COVID -19, which is the most severe infection associated with pregnancy complications. (15)

These studies indicate that pregnant women with SARS-CoV-2 infection have a significantly increased risk of maternal death, admission to the ICU, preterm birth, and stillbirth compared with those without SARS-CoV-2 infection. Moreover, infants born from mothers infected with SARS-CoV-2 were more likely to be admitted to the neonatal ICU than those born from mothers without the disease. (14)

Álvarez Bartolomé and Collaborators, in a prospective multicenter study recruited 1347 SARS CoV 2 infected pregnant women at the first wave of the pandemic- They investigated the causes and risk factors for ICU admission. The incidence of ICU admission in this series was 2.6% before giving birth. The main causes were non-obstetric causes:40% were worsening of maternal condition and respiratory failure due to SARS CoV 2 pneumonia and 31.4% due to a combination of COVID 19 symptoms (pneumonia) and obstetrical complications: PE, hemorrhagic events, thromboembolic events, and disseminated intravascular coagulation. In the group of pregnant women admitted to the ICU, they observed a higher proportion of symptomatic patients, lower GA, women requiring in vitro fertilization, and a higher rate of multiple pregnancies. When pneumonia coexists with PE, the risk of requiring intensive care exponentially increases. The high rates of PE could be explained by the excessive inflammation produced by cytokine release and the increase in the vasoconstrictor angiotensin II. (16)

Preeclampsia (PE) is a pregnancy complication and an important source of maternal and fetal morbidity and mortality, which can cause poor perinatal outcomes and iatrogenic prematurity. PE complicates 2-4% of pregnancies. Its etiology is not fully understood, but it is based on placental insufficiency and maternal cardiovascular maladaptation due to angiogenic imbalance, endothelial dysfunction, coagulopathy, and inadequate complement regulation. It manifests clinically as the onset of hypertension, proteinuria, or multiorgan dysfunction during pregnancy. Depending on the

gestational age at onset (early or late), both clinical and laboratory findings may vary. (17) Most of the clinical manifestations of PE show similarities with the symptoms presented by patients with severe COVISD 19 disease.(10)

The risk of PE associated with SARS COV 2 infection has generated multiple meta-analyzes, systematic reviews, cohort studies, case reports as it is considered a public health topic that requires specialized clinical management to prevent poor pregnancy outcomes (9,10,12)

Some publications on the evolution of the disease during pregnancy and obstetrical and neonatal outcomes reported no significant association with PE (18)

The meta-analysis of Conde Agudelo which included 15524 pregnant women infected for SARS CoV-2; their main objective was to establish the relationship between SARS-Cov-2 during pregnancy and the occurrence of PE. They showed that SARS-CoV-2 infection during pregnancy increased the risk of preeclampsia by 62% when compared with pregnant women without infection (pooled odds ratio, 1.62; 95% CI, 1.45-1.82; P<.00001; I2 17%). This increase in PE was observed in both symptomatic and asymptomatic pregnant women, but was more frequent in symptomatic women. (2.11 95% CI 1.59-2.81 vs 1.59 95% CI 1.21- 2.10).

This association remained significant after adjusting for confounding risk factors, such as maternal age, body mass index, pre-existing comorbidities, and ethnicity. Nevertheless, they affirmed that pre-existing risk factors are not sufficient to explain the relationship between COVID 19 and PE. This study confirmed that pregnant women with SARS-Cov-2 infection are more likely to develop PE. (9)

Prior to the onset of vaccines, other authors also noted that symptomatic COVID -19 pregnancy patients were shown to have worse outcomes than asymptomatic patients, especially those with severe symptoms, where a higher risk of preeclampsia was observed compared with asymptomatic patients (OR 2.11 (95% CI 1.59 - 2.81) vs. OR 1.59, 95% CI 1.21 - 2.1) (13)

The INTERCOVID group in their multinational cohort study involving patients of 43 institutions in 18 countries also reflected in their results comparing pregnant women diagnosed with COVID 19 with undiagnosed pregnant women with COVID 19 that the risk of maternal morbidity and mortality, specifically PE, was higher in those with symptoms (especially respiratory symptoms of several days of evolution) compared to asymptomatic patients. PE OR 1.76 (95% CI, 1.27-2.43) vs 1.63 (95% CI 1.01- 2.63) (19)

Jonathan Lai et al proposed to observe the association between the severity of SARS Cov 2 infection and the probability of PE. This was a retrospective, observational study. They included 1223 pregnant women with COVID 19 and PE divided into four groups: asymptomatic, mild, moderate and severe COVID 19. The a priori risk for developing PE was 1%. The risks obtained were 1.9%, 2.2 %, 5.7 %, and 11.1% for asymptomatic, mild, moderate, and severe disease, respectively. They also reported that the median interval between the diagnosis of preeclampsia and the onset of SARS-CoV-2 infection was 16 days (interquartile range, 7–61 days). The main findings reported a dose-response relationship between the severity of SARS-CoV-2 infection and the risk of developing preeclampsia or preterm delivery. The frequency of PE increased as the severity of COVID 19 increased. (20)

When comparing the odds of PE in relation to gestational age at infection, Badr et al. recruited 393 pregnant Cov-2 positive SARS patients from 10 weeks of GA to term gestation. Their primary outcome was to compare adverse maternal and fetal outcomes relative to the timing of infection during pregnancy; other secondary outcomes were found to increase the risk of PE, eclampsia, and HELLP. Obstetric outcomes were worse when the infection was acquired after 20 weeks, and perinatal outcomes were unpleasant when the infection was acquired after 26 weeks. Therefore, vaccination should be administered as soon as possible after the diagnosis of pregnancy. (21)

Rosenbloom estimated the time between the onset of both entities (COVID 19 and PE) and observed that when infection appeared after 32 weeks of pregnancy, there was less association with PE than when infection occurred before 32 weeks of pregnancy OR 2.88 vs 2.74. This association was statistically significant only before week 32. The same author published that 3.79 weeks elapsed from SARS CoV 2 infection to the appearance of PE, therefore SARS infection in pregnancies at term did

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not give time to develop PE. According to other authors, the risk of PE persisted regardless of the gestational age at the time of SARS CoV 2 infection. (22)

In a multicenter prospective observational study carried out in 78 Centers of Spain, Cruz Melguizo et al. analyzed a cohort of 1347 SARS CoV 2 PCR + pregnant women compared with 1607 PCR-negative women (testing by universal screening for a SARS CoV 2 infection at admission to the delivery ward). This study aimed to better understand the relationship between maternal infection and prenatal outcomes. The main differences observed between both groups were PROM (15.5% vs. 11.1%), venous thrombotic events (1.5% vs. 0.2%), and severe PE incidence (40.6% vs. 15.6%, OR 3.69, 95%CI 1.62- 8.39 p< 0.001). They affirmed that the incidence of PE could have been overestimated in the infected cohort because the analytical signs of COVID 19 could have been interpreted as alteration due to PE instead, apart from the inflammatory status present in both conditions. Although 51.1% of symptomatic patients were asymptomatic at delivery, 3.9% showed complicated pneumonia upon ICU admission. (23)

Can the association between COVID 19 and PE be explained?

Several theories have been considered to explain the association of COVID 19 with PE; most likely, it is not the product of a single mechanism but the association of several of them: (24)

1. Direct effects of the virus on trophoblastic function and on the arterial wall include endothelial damage and dysfunction
2. Acute atherosis. Atherosis is a specific lesion of the spiral arteries that is equivalent to atherosclerotic lesions observed in the coronary arteries.
3. Local inflammation leading to placental ischaemia
4. Indirect effect in response to exaggerated inflammatory responses in pregnant women. (cytokine release syndrome IL 6)
5. To date and in line with recent and ongoing research SARS Cov 2 related myocardial injury (25,26,27)
6. Cytokine storm IL 6
7. The thrombotic microangiopathy (TMA)

The door is the clue

Coronavirus disease 2019, a historic pandemic, has potential cardiovascular health consequences for millions of people who survive the infection worldwide. SARS-CoV-2 can infect the heart, vascular tissues, circulating cells, and maternal and fetal cells in the placenta (trophoblast and cytotrophoblast). (28) Virus enters the cell after the N-terminal portion of the viral spike protein (S) through angiotensin-converting enzyme 2 (ACE2), the host cell receptor for the viral spike protein. ACE2 is an important component of the renin-angiotensin system (RAS), which converts angiotensin II to angiotensin 1 to 7. RAS is a regulator of placental function and plays an important role in controlling trophoblast proliferation, angiogenesis and blood flow. RAS markedly modulates uteroplacental blood flow through stabilization of its vasoconstrictor and vasodilator pathways.(29) Binding of SARS-CoV-2 to ACE2 receptors results in downregulation of the RAS system, lowering vasodilatory angiotensin levels from 1 to 7, unopposed by the pro-inflammatory and vasoconstrictive effects of angiotensin II. These alterations in the RAS may play a role in the pathophysiology of PE. (30)Susceptibility to viral infection throughout pregnancy is variable; Bloise et al. demonstrated that ECA2 cell expression is dependent on gestational age and is higher in the first trimester. (31)

Verma et al. describes how SARS CoV 2 Infected placentas show a significant reduction in ACE 2 receptors, which causes an increase in the production of the soluble form of tyrosine kinase 1 (sFlt-1) and a decrease in proangiogenic factors. Serum levels of sFlt-1 and autoantibodies versus angiotensin II type 1, both PE markers, are increased in pregnant women infected with SARS-CoV 2 when compared to uninfected women. These findings reaffirm a possible mechanism involved in the association between COVID 19 and PE. (28)

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Palomo et al. compared the expression of markers of endothelial damage, coagulopathy, and angiogenic imbalance both in vivo and in vitro with the aim of establishing their function in pregnant women with COVID 19, pregnant women with PE, and healthy controls. They concluded that although they are similar, each presents a different pattern that could differentiate between the two diseases (COVID 19 and PE). (32)

Given that COVID 19 and PE manifest overlapping clinical features, a differential diagnosis must be established to ensure correct management. Along these lines, the work of Mendoza et al and other authors described a syndrome similar to PE in pregnant women with COVID (Pre-eclampsia like syndrome) warning that these patients should not be delivery prematurely to prevent worsening of neonatal outcomes when treating them as PE. (33, 34)

Both diseases have an associated pro-inflammatory state called cytokine storm. This is a risk factor for a more severe disease. In both cases, the proinflammatory enzymes IL-6, TNF alpha, and serum ferritin are elevated. The proinflammatory state in COVID -19 infection may be associated with hypoxic damage to the placenta and consequently the appearance of PE, may also favor intrauterine growth retardation and preterm delivery (35)

COVID 19 and PE are not the only similar entities. As described in the reports of pre-pandemic studies, several disorders have previously been shown to imitate PE because they present similarities in clinical and laboratory findings. They also share physiopathology causes, such as endothelial cell dysfunction, platelet activation, microvascular thrombosis, vasospasm, and reduced tissue perfusion. Some of these disorders include gestational hypertension, acute fatty liver during pregnancy, hemolytic uremic syndrome, chronic kidney disease, acute exacerbation of systemic lupus erythematosus, thrombotic thrombocytopenic purpura, severe hypothyroidism, and sepsis. These similarities suggest that although there is a common basis for the two pathologies, they should be differentiated to administer appropriate treatment so as not to cause morbidity in the pregnant woman or her child. (36)

Interleukins as possible explanation

IL-6 is one of the cytokines more studied both in human parturition and in adverse pregnancy conditions. Referred sometimes as a causal factor for adverse outcomes such as infection and inflammation associated with preterm birth and pPROM. (37)

IL-6 is a pro-inflammatory cytokine that regulates both acute and chronic inflammatory responses in autoimmunity and endothelial cell dysfunction. It is an independent risk factor for cardiovascular diseases. (38)

SARS CoV-2 infection is transmitted mainly through the upper respiratory tract, where it begins to stimulate the immune system and progresses to the lower respiratory tract, where it replicates, generating various alarm signals. As explained above, the viral S glycoprotein is the “key protein” that enters cells using the ACE-2 receptor, which is expressed in the epithelial cells of the pulmonary alveoli, endothelium, and alveolar macrophages. (29, 38,39)

Alveolar immune effector cells are activated and release proinflammatory cytokines such as IFNα, IFNγ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNFα, TGFβ and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3, CCL5). SARS-CoV-2 induced disease mainly occurs because of an excessive response from the host immune system with respiratory and multiorgan repercussions.

IL-6 opts for a pro-inflammatory activity when there is no control over its production, so an excessive assembly of this cytokine can be a pillar for pathogenesis of cytokine release syndrome (38, 39)

Laboratory studies have shown that there is no passage of IL 6 through the placenta and this, together with the very low transplacental transmission of SARS CoV-2, leads us to conclude that the placental barrier is an effective defense against the consequences of the COVID 19 cytokine storm in the fetus (40)

In the pathogenesis of PE, a similar mechanism has been described where an aberrant systemic inflammatory response triggered by placental stress can cause systemic involvement with fatal maternal or neonatal outcomes. In preeclampsia, maternal levels of inflammatory mediators, such as

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inflammatory cytokines IL-6, IL-8, tumor necrosis factor (TNF), intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule-1 (VCAM-1), and P-selectin are elevated. (41)

These findings support the concept of an increased systemic inflammatory response in preeclampsia, this state is considered to play a significant role in the vascular dysfunction. Endothelial dysfunction, persistent leukocyte and platelet activation, and elevated inflammatory cytokine levels are all considered hallmarks of an increased inflammatory response in this pregnancy disorder. An increased inflammatory response contributes to oxidative stress and vasoconstriction, with consequent multiorgan involvement shared by the two entities. (41,42)

In a meta-analysis by Agudelo et al., the principal finding was that there was a dose-response relationship between the severity of SARS-CoV-2 infection and the risk of subsequent development of preeclampsia and preterm birth. (9) Therefore, severe SARS CoV2 infection indirectly affects pregnancy by triggering a vascular pathology typical of gestation, such as preeclampsia, which affects the patient's prognosis.

Thrombotic microangiopathy, COVID 19 and Preeclampsia

In coagulopathy, coagulation takes place by activation of coagulation on the one hand and fibrinolytic cascades on the other. In cases of COVID 19 probably triggered by viral sepsis, activation of coagulation causes the consumption of clotting factors. Manifestations can be either thrombotic or hemorrhagic. When associated with pregnancy, the process is more complex because of its physiologically hypercoagulable state, with an increase in coagulation factors, such as fibrinogen and D-dimers. (43)

Thrombotic microangiopathy (TAM) is comprised of a group of diverse entities that deal with thrombocytopenia, microangiopathic hemolytic anemia, and multiple organic dysfunction syndromes. All of these conditions are characterized by a high rate of morbidity and mortality. The main protagonists of the pathogenesis are endothelial damage and microthrombosis, which cause platelet consumption, destruction of red blood cells by fibrin filaments, and ischemia of organs and tissues due to vascular occlusion. Disseminated intravascular coagulation (DIC) occurs in parallel. (44)

TAM is typically divided into primary and secondary. Primary disease includes hemolytic uremic syndrome (HUS) with predominant renal involvement and thrombotic thrombocytopenic purpura (TTP) with multiple organic dysfunction syndrome. Secondary TAM is associated with a large number of systemic conditions such as pregnancy, infections, severe hypertension, connective tissue disease, cancer, and autoimmune diseases. Secondary TAM may also develop after organ transplantation or may be caused by taking some medications. (44)

A non-negligible number of complications of pregnancy and postpartum period can lead to development of TMA. The most dangerous of these are preeclampsia, eclampsia, and the HELLP syndrome. Pregnancy can trigger the development of primary TMA in patients with an existing predisposition. (43)

It is well documented that viral infections play an important role in the development of thrombotic microangiopathy. The virus can directly injure endothelial cells by inducing the expression of endothelial adhesion molecules, the release of von Willebrand factor (vWF), platelet adhesion, or the activation of alternative pathways (complement), resulting in TMA. The exact mechanism of viral microangiopathy remains unclear, but direct damage to the endothelial wall appears to play an important role. (45)

There is emerging evidence that infected COVID -19 patients admitted to hospitals have a hypercoagulable state. Given that pregnancy itself has a hypercoagulable shift, it can be suggested that COVID -19 infection during pregnancy is associated with a high risk for maternal thrombotic complications. This is particularly true in pregnant women with antiphospholipid antibodies, secondary infection, thrombotic microangiopathy, sepsis, comorbidities, and other severe obstetric complications. Inflammation also perpetuates a hypercoagulative state, mediated by endothelial cell damage which causes thrombosis. Fibrinogen levels are elevated in response to high IL-6 release

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(cytokine storm), and fibrin clots are formed after conversion to fibrin in the presence of thrombin, generating unwanted microthrombi. (46)

A massive release of Von Willebrand Factor (vWF) from endothelial cells, as it occurs in severe inflammatory states and systemic infections, can lead to a mild decrease in vWF-cleaving protease, a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13). Whether the resulting vWF/ADAMTS13 dysregulation contributes to the pathophysiology of certain TMAs in a similar way as in classic TTP is characterized by a very severe deficiency of ADAMTS13 activity (<5–10% of normal). (47)

Complement deposits have also been demonstrated in the lungs and skin of patients with COVID 19, co-investing in another possible pathway of activation of thrombotic phenomena. Histological examination of these patients revealed C5b-9, C4d, and MASP2 complement complex deposits in the lung and skyn microvessels. The formation of complement complexes is followed by activation of the hemostatic system with the formation of fibrin blood clots. At the same time, there was a sharp increase in the blood levels of D-dimer. (46)

According to the recommendations of the International Society of Thrombosis and Hemostasis (ISTH, 2020), a preventive dose of low-molecular-weight heparin (LMWH) should be prescribed to all patients (including non-critical patients) who require hospitalization for COVID -19 in the absence of any contraindications. (48)

In summary, given that the literature published in the wake of the COVID -19 pandemic is forceful in pointing to thrombotic complications as a primary cause of morbidity and mortality observed in severely affected patients, including pregnant women, the use of prophylactic or therapeutic doses of anticoagulants is recommended. However, in some patients, this therapy is ineffective in preventing thrombotic complications, suggesting that additional mechanisms, such as TAM.

Angiogenic and antiangiogenic factors are differential markers in Preeclampsia

Placental dysfunction underlies a spectrum of perinatal pathologies, including preeclampsia and fetal growth restriction. Several angiogenic factors are implicated in placental dysfunction: VEGF-A (vascular endothelial growth factor A) is essential for placental vascular development and influences vascular permeability as well as proliferation and migration of endothelial cells; placental growth factor (PlGF), a proangiogenic VEGF family member, is profusely expressed in the placenta and acts by amplifying the action of VEGF-A; and sFlt-1 (soluble fms-like tyrosine kinase 1), an antiangiogenic VEGF family member, is a key factor in the control of angiogenic homeostasis during pregnancy. Both sFlt-1 and PlGF are expressed in placenta, vascular endothelial cells, osteoblasts, smooth muscle cells, fibroblasts, and monocytes. (49)

Any variation in the proportion of pro-angiogenic factors (i.e., increased sFlt-1/PlGF ratio) produces an anti-angiogenic state that favors the development of placental dysfunction (36), and abnormal serum levels of angiogenic factors sFlt-1 and PlGF reflect placental dysfunction and may be altered weeks before a pregnancy complication occurs. A normal ratio of sFLT-1:PlGF in women with clinical suspicion of preeclampsia can be reliably used to predict the absence of short-term onset of PE (50)

It has been well established by multiple studies the utility of the Flt-1/PlGF ratio for prediction, diagnostic aid tool, monitoring and discarding of PE before the pandemic (50) this diagnostic laboratory tool was used during the pandemic in pregnant women infected with SARS Cov-2 and clinical suggestive of PE to try to differentiate the two entities. In some studies, these markers were found to be altered in patients with severe COVID and symptoms of PE, and in others, it was not possible to correlate the alteration of their values with the appearance or severity of PE (51).

Giardini et al. included 57 pregnant women, who were divided into those with signs and symptoms of COVID -19 at hospital presentation (n = 20, 35%) and asymptomatic women (n = 37, 65%). The sFlt-1/PlGF ratio was stratified using cut-off values clinically utilized for PE prediction (low risk, < 38; high risk, > 85 if before 34 weeks of 'gestation or > 110 if after 34 weeks' of gestation). They found high levels of sFlt-1 in asymptomatic patients, but the sFlt-1/PlGF ratio was less than 38;

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on the other hand, the sFlt-1/PlGF ratio was elevated in symptomatic patients (decrease of angiogenic factors), and there was no difference in PE cases between the two groups. Gestational age at the time of infection seems to influence this outcome; the lower the GA, the higher is the ratio. (52)

Soldavini et al. found significantly higher sFlt-1/PlGF ratios in non-COVID -19 patients with hypertensive disorders of pregnancy (HDP) than in COVID -19 patients with both hypertensive and normotensive statuses. That is, higher ratios in patients with HDP regardless of their COVID status suggesting independent pathways of inflammation and angiogenic balance in these cases. Placental biomarkers were not correlated with the severity of symptoms, except for severe respiratory failure.(53)

Espino-y-Sosa, found that the sFlt-1/PlGF and sFlt-1/ANG II ratios were elevated in pregnant women with COVID 19 pneumonia; this elevation was a marker of poor evolution, and the sFlt-1/ANG-II ratio was associated with an increased probability of severe pneumonia (odds ratio [OR]:1.31; p = 0.003), ICU admission (OR:1.05; p = 0.007), intubation (OR:1.09; p = 0.008), sepsis (OR:1.04; p = 0.008), and death (OR:1.04; p = 0.018). However, this was not associated with PE complications. (54)

Studies in non-pregnant populations have already described the elevation of serum sFlt-1 levels in patients infected with SARS Cov-2 and its importance as a marker of poor prognosis, especially thrombotic events, encouraging physicians to establish more aggressive therapy in patients with elevated sFlT-1 to improve their survival. (55)

As previous mentioned, Mendoza et al. reported that severe cases of COVID -19 infection induce the development of a preeclampsia-like syndrome. It can be distinguished from true preeclampsia when ultrasound shows the normal uterine artery pulsatility index (PUtI) and sFlt-1/ PlGF ratio in normal parameters. The abnormal sFlt-1/PlGF ratio in these cases does not reflect abnormal placentation but is a clinical manifestation of severe infection. In addition, markers normalized in COVID -19 infected pregnant women before delivery of the placenta, reflecting the absence of placental dysfunction. (33)

As described in other studies that used the sFlt-1/PlGF ratio to try to differentiate PE from other diseases of pregnancy with similar clinical conditions, such as chronic renal failure (CKD) in cases of COVID 19 and PE, it seems that determining the ratio alone does not seem to be a useful tool to differentiate between these two entities; analyzing the evolution of the clinical situation, as well as associating other parameters such as PI of uterine arteries is more useful. (56)

Maternal cardio vascular dysfunction.

Current evidence supports the role of maternal cardiovascular dysfunction in preeclampsia genesis. Most of this evidence is derived from studies that have found an increased risk of both PE and fetal growth restriction in women with congenital heart disease compared to healthy pregnant women. (25, 26, 57)

PE is associated with a higher prevalence of asymptomatic left ventricular dysfunction and myocardial injury when compared with cardiovascular function in normotensive pregnant women (58) Diastolic dysfunction and left ventricular remodeling are more pronounced in severe early onset preeclampsia, can be detected before clinical manifestation and are associated with adverse pregnancy outcomes. Abnormalities in PE reflect a multisystem disorders. (59)

During the preclinical phase of preeclampsia, the total peripheral resistance index, sFlt-1, and B-type natriuretic peptide (BNP) levels are elevated. A combined model using these parameters was successful in differentiating preeclampsia cases from controls with very high precision (area under the curve,0.96). These findings suggest that, prior to the onset of clinical PE, peripheral vasculopathy and excessive tension in the ventricular walls lead to elevated BNP levels. These effects are most noticeable in early onset PE, suggesting more severe cardiac involvement. (60)

Although the placenta is considered to be a temporary, single organ, there may be an overlap of pathophysiological mechanisms leading to dysfunction in other organs in patients with heart failure. The synergy between maternal hypoperfusion, increased central venous pressure, pre-existing

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hypertension and chronic hypoxia leads to placental dysfunction manifested as hypertensive disorders of pregnancy causing adverse obstetric and neonatal outcomes.(27,61, 62)

On the other hand, several studies have described the deleterious effects of COVID 19 on the cardiovascular (CV) system; in elderly patients with comorbidities CV involvement is common, but in adult patients with severe COVID 19 without previous comorbidities it has been described acute myocarditis too.(63) The exact mechanism underlying cardiac involvement in COVID -19 remains unclear. One possible mechanism is direct ACE-2-mediated myocardial involvement. During the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of the autopsied hearts. Other suggested mechanisms of COVID -19-related cardiac involvement include a cytokine storm mediated by an unbalanced response between T-helper cell subtypes and hypoxia-induced excess calcium which would lead to apoptosis of cardiac myocytes. (64)

In non-pregnant women infected with SARS Cov-2 severe disease has been associated with myocarditis, acute myocardial infarction, cardiomyopathies, arrhythmias, and venous thromboembolic events (65), and myocardial damage is considered the most frequent CV event and is an independent risk factor associated with high mortality, 5 times more needing mechanical ventilation, and 11 times more deaths. Myocardial damage is defined as an elevation in cardiac troponin concentration above the 99th percentile. (66)

Although there are several mechanisms can cause myocardial damage, myocarditis and systemic inflammation are the most common. Myocardial damage is considered a mortality risk marker, more so than age, previous CV disease, CV risk factors, and chronic lung disease. All patients had elevated levels of serological markers of myocardial damage (BPN) and troponin. (65)

These findings raise the possibility of a higher prevalence of COVID -19 induced systolic dysfunction in pregnant women compared to non-pregnant patients.(67)

To understand the impact of COVID 19 on the hearts of pregnant women, Mercedes et al. conducted a retrospective study of 15 previously healthy pregnant women with confirmed COVID 19 that developed myocardial injury. All patients were admitted to the ICU. Myocardial injury was confirmed by highly elevated troponin serum levels (> 0.4 ng/mL) (AA) and Pro-B-type natriuretic peptide concentration in addition to structural and functional worsening of the left ventricle, as diagnosed by transthoracic echocardiography. All patients presented with LV dysfunction, with a mean LVEF of 37.67%±6.4 (normal value >50%), and LV diffuse hypokinesis. These findings suggest a higher prevalence of COVID -19 induced systolic dysfunction in pregnant women compared to non-pregnant patients.(54) Cardiovascular dysfunction in pregnant women who are critically ill due to COVID -19 is associated with an increased maternal mortality rate (13.3%).(68)

Jusela et al describes two cases of previously healthy pregnant women with COVID 19 who developed cardiomyopathy: they presented cardiovascular (CV) dysfunction with moderate reduction in left ventricular ejection fraction (40-45%) and hypokinesia. Whether ventricular dysfunction results from direct virus effects on cardiac cells or from multiple organ failure cannot be known with certainty in these patients. It is important to diagnose CV involvement to treat them properly and prevent complications.(69)

Another authors, although the population of pregnant women with coronavirus was limited, found among the pregnant women admitted to the ICU and who presented hypertension or PE elevation of the serum concentration of Troponin I -cTn and pro B-Type natriuretic peptide and bradycardia as expression of myocardial injury (67,69)

In view of the evidence of cardiac involvement that exists in both severe SARS Cov-2 disease and Preeclampsia , it has been proposed and we share this approach, the possibility that the increased incidence of Preeclampsia observed during the pandemic in pregnant patients with severe COVID 19, derives from myocardial dysfunction that occurs in this disease (related to a massive systemic inflammation or damage of cardiomyocytes by direct entry of the virus to cells). Pregnant women with severe COVID -19 disease would have heart disease and myocarditis, and the latter conditions generate hypoperfusion and acquired ischemia both in the placenta and possibly in other organs. Hypoperfusion and ischemia lead to an imbalance in the production of pro- and anti-angiogenic factors with subsequent development of preeclampsia (27, 62, 70)

This hypothesis that myocardial injury related to SARS-CoV-2 infection could explain the development of preeclampsia in infected pregnant women is interesting and is proposed as a topic for future research (71).

Conclusions

Pregnancy is a risk factor for developing severe COVID 19 in unvaccinated pregnant women, especially those with comorbidities.

There are several common pathophysiological mechanisms between coronavirus 2 disease and PD, it has been shown that there is an association between SARS Cov-2 infection and PD that could be causal.

Symptomatic respiratory patients and/or patients with more severe coronavirus disease were those at higher risk of developing PE

There is insufficient evidence to state whether the timing of infection during pregnancy was associated with a higher risk of developing PE although the most severe cases were observed when the two pathologies coincided at the end of the second trimester and during the third trimester increasing worse obstetrical and neonatal outcomes.

It is entirely plausible that the complex relationship between SARS-Cov-2 infection and acute severe cardiovascular dysfunction that has been described in COVID -19 patients may also occur during SARS-CoV-2 infection in pregnancy. The results of these studies are similar to this hypothesis. This may be related to massive systemic inflammation that has been confirmed by elevated levels of troponin and pro-B natriuretic peptide, and left ventricular dysfunction, both in and outside pregnancy. Myocardial injury and subclinical cardiovascular dysfunction leading to acquired uteroplacental malperfusion and ischemia may lead to preeclampsia in symptomatic and asymptomatic pregnant women.

Restoration of the immune balance in Preeclampsia , which may be a potential strategy for the development of therapeutic interventions that could improve maternal and fetal outcomes associated with this maternal syndrome.

Vaccination against COVID -19 in the general population and in pregnant women in particular, dramatically reduced the severity of the disease. There is an urgent need to follow up these women and infants because of possible long-term health effects, including long-term COVID -19

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