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Mini Review

THE IMPACT OF COVID-19 ON PREGNANCY OUTCOMES AND ITS EFFECTS ON OXIDATIVE STRESS – MINI REVIEW

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ABSTRACT

Viral infections during pregnancy are not uncommon and may cause different complications both: 1) on the fetus; depending on which trimester when the woman gets infected, in addition to the 2) maternal complications.

During the last decades, several cases of coronavirus like SARS, MERS have been identified in different regions of the world especially in the Middle East and Africa. According to the clinical experience of pregnancies that were complicated with infection by these types of coronaviruses, has led to pregnant women being considered potentially vulnerable to severe SARS-CoV-2 infection.

The impact of SARS-CoV-2 in pregnancy remains to be found , and researches are required to determine the effects on implantation, fetal growth and development, labor, and neonatal health and the role of the infection during pregnancy on the oxidative stress.

Keywords: pregnancy, covid-19, preeclampsia, LBW, preterm, oxidative stress

INTRODUCTION

A series of a new coronavirus pneumonia (NCP), whose pathogen is the novel 2019 coronavirus (2019 - nCoV) was officially recognized by the World Health Organization on February 11, 2020 and the disease was called COVID-19 (CoV-19). The International Committee on Taxonomy of Viruses named the 2019 novel coronavirus as CoV-2. On March 30, 2020, approximetely 82,447 confirmed cases and 3,310 deaths were reported in China, with a case fatality rate of~ 4.0%, at the same time there were 693,224 confirmed cases and 33,106 deaths worldwide, and a case fatality rate of~ 4.8%. It was clear that the epidemic was spreading globally.

WHO has raised the global risk of the CoV-19 epidemic to the highest level (*very high*). CoV-19 virus and the other two highly pathogenic coronaviruses, the SARS- and MERS- CoV. SARS-CoV-2 gives rise to a global threat to public health.

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Pregnant women are particularly vulnerable to respiratory pathogens and developing pneumonia is one of the serious complications during pregnancy. This is due to physiological and immunological changes, like: altered T-lymphocyte immunity, elevated diaphragm, decreased chest compliance, decreased functional residual capacity, and increased oxygen consumption, hence pregnant women are more susceptible to hypoxia and airway odema. These changes will lead to a significant increase in maternal and fetal morbidity and mortality. Pregnant women with pneumonia have a significantly higher risk of giving birth to low birth weight, preterm and small for gestational age ,infants with low Apgar scores, born by cesarean section as these pregnant women presented with preeclampsia/ eclampsia more often than uninfected women (1-3).

Coronaviruses are single-stranded RNA, nonsegmented, enveloped viruses, they cause diseases ranging in severity from the common cold (treated conservatively) to severe conditions that need ICU admission and may end fatally. The coronavirus name is derived from the Latin word *corona*, which means

crown or halo; that the nomination arises from the appearance of coronavirus virions visualised by electron microscopy, in which the virus particles have a crown-like fringe typically referred to as spikes (4).

A nonsystematic search of academic databases (PubMed, Web of Science, ScienceDirect, Google Scholar) and grey literature (Google) was performed to extract and synthesize relevant studies that describe the effect of SARS-Co-2 on the pregnancy and the role of oxidative stress (OS) during the infection.

Pathogenises

The COVID-19 (CoV-19) structure is described as a positive single stranded RNA genome characterised by four genes; a spike protein, an envelope, a membrane and a nucleocapsid. The virus target is the pulmonary area. The virus binds to the host receptor, the angiotensin converting enzyme 2 (ACE_2) via receptor binding domains. After the binding to the receptor of the host cell, the spike protein undergoes a modification in the configuration for the viral envelope to bind to the cell membrane for RNA release into the host cell (5). This process happens via the endosomal pathway. Once RNA enters the host cell, it is translated into viral replicases, they split into smaller particles by enzymes called proteinases. The particles will be translated into viral proteins through mRNAs and foregathered into virions on the endoplasmic reticulum and the Golgi apparatus where they are released out of the cell via vesicles. After particles release, they enter the alveoli cells, endothelial cells and blood cells. This will lead to exaggerated activation of immune cells and cytokines (5). The immune response in normal pregnancy will be shown as an increase in the NKG2A, ACE_2 receptors, and increase pro-inflammatory factors. On the other hand, there is a decrease in lymphocytes and in natural killer cells.These changes can be seen also in patients with CoV-19 (5).

Pregnancy is an immunosuppressive state in which the women are particularly susceptible to respiratory pathogens and severe pneumonia The physiological adaptive changes during pregnancy turn them intolerant to hypoxia. It was found that pregnant women were more likely to be admitted to hospital for the 2009 H_1N_1 flu four-fold than the general population. According to a previous report, 50% of pregnant women with CoV-19 are sent to intensive care a unit, 33% of pregnant women with SARS need mechanical ventilation, and the death rate of these women was ~ 25%. Nevertheless, pregnant women with CoV-19 pneumonia showed a similar pattern of clinical characteristics to non-pregnant adult patients, as recently reported (5, 6).

The SARS-CoV-1 outbreak during 2002-2004 was linked to complications such as severe infection and a higher mortality rate in pregnant women compared to non-pregnant patients. Similarly, an increased risk for severe CoV-19 among pregnant women compared with non-pregnant women has also been reported. SARS-CoV-1 also leads to different obstetric complications like spontaneous abortion, preterm delivery and intrauterine growth restriction (7). Importantly, animal models showed that expression and activity of angiotensin-converting enzyme 2 (ACE_2), the main receptor for SARS-CoV-2, increase in kidney, uterus and placenta during pregnancy. Accordingly, it can be speculated that reproductive organs are potential targets for SARS-CoV-2. The impact of SARS-CoV-2 infection on pregnancy outcomes have not been consistently reported (7). Pregnant women infected with CoV-19 were reported to show increased rates of obstetric complications like caesarean delivery and preterm birth. Although, there are reports, hat indicated no significant difference between CoV-19 infection, and adverse outcomes of pregnancy. (7) The vertical transmission from the mother to the fetus or neonate during perinatal period is another problem that needs to be studied. Since the beginning of the CoV-19 outbreak, several studies have been published regarding mother-to-infant transmission but the risk of vertical transmission (8) in the population is not clear. Unfortunately, the absence of knowledge and anxiety in patients and clinicians could explain the high rate of preterm birth and caesarean delivery in CoV-19 patients. In different studies, data are provided regarding the rate of vertical transmission, CoV-19 detection in neonates born to infected mothers, and viral detection in breast milk and conception products. In this review, we do analysis of reports on CoV-19 infection and its impact on oxidative stress and pregnancy outcomes.

We aimed to provide a comprehensive review regarding pregnant patients (8). We analysed clinical, laboratory and imaging features of the CoV-19 infection in addition to pregnancy-

related characteristics and outcomes of pregnant women and the changes in OS levels.

Oxidative stress in pregnancy and during CoV- 19 infection

OS is an imbalance between antioxidants and pro-oxidants in antioxidants' favour. Antioxidants have an important role in protecting against molecular damage. Pregnancy exhibits different complications that can be related to OS changes, also associated with the development of different pathologies. OS is considered a risk factor during pregnancy (9). During the first trimester, the pregnancy induced nausea and vomiting especially the severe condition (hyperemises gravidarum) suggests that the evaluation of markers of total oxidant/ antioxidant status could be effective as an additional diagnostic of this clinical complication **(Figure 1).**

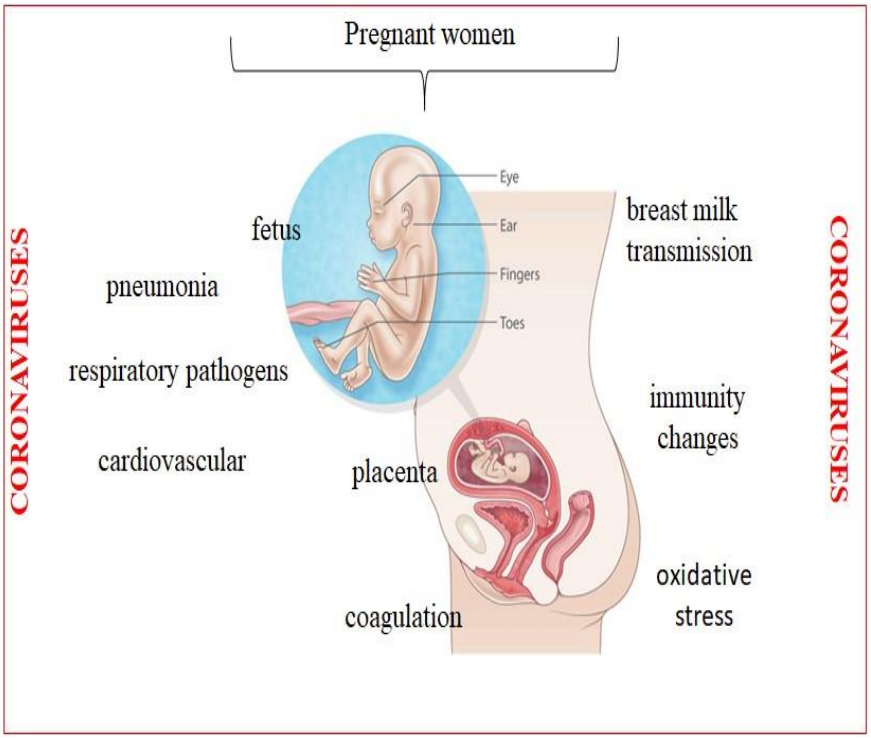

Figure 1. Pregnancy and COVID-19 complications.

While the development of gestational diabetes and fetal macrosomia are associated with a decrease in antioxidant regulation as macrosomia is associated with changed lipid metabolism. Increased OS is a widely considered participant in the development and progression of diabetic tissue damage and the changes in the antioxidant enzymes activities in various tissues (9). Other complications like PIH (pregnancy induced hypertension) which include preclampsia, gestational hypertension and eclampsia are major causes of maternal mortality and morbidity, and are often the cause of premature birth and high cesearean section rates. OS probably is one leading factor in this pathology. The lipid peroxidation elevation, especially in malondyaldehyde (MDA) in pre-eclamptic woman, decreased antioxidant defenses (10).

Common factors are observed for OS and the CoV-19 infection. Various risk factors are associated with the severity and mortality of SARS-CoV-2, and elevated OS enhancing the CoV-19 severity. Antioxidant supplementation use may decrease this severity. Viral pneumonia is caused by CoV-19 induced overstimulation of immune response in the lung tissues initiated by viral replication. This pathological process is always associated with OS. CoV-19 is capable to causing pneumonia that can be severe as it leads to Pneumocytes type-2 infection (11). Pneumocytes type-2 have a large number of mitochondria synthesizing acetyl-CoA that is used to make fatty acids and phospholipids, which are important elements of pulmonary surfactants on the epithelial cells surface. Unfortunately, it remains unclear whether CoV-19 triggers OS in the lung epithelial tissue. However, patients with moderate and severe CoV-19 sometimes develop respiratory distress neutralized by oxygen therapy that could lead to OS and ARDS (11, 12). Hypoxia induced reactive oxygen/nitrogen species (ROS/ RNS)

generation in mitochondria and originates inhibition in oxidative phosphorylation and lowering ATP levels (12).

Normal pregnancy is a physiological process that includes multiple transient complex changes, such as decidual, placental formation, and fetal delivery. These changes are significant for a normal pregnancy and any changes may lead to complications in the mother and fetal health. Pregnancy is known to increase OS, generated by a normal systemic inflammatory response, and causing induction in the circulating ROS/ RNS. The main ROS/ RNS origin during pregnancy is the placenta. ROS/ RNS could be found at the decidual, trophoblast and mesenchymal parts in the maternal-foetal interface (12, 13). Physiological ROS/ RNS production is crucial for signalling, regulation of redox-sensitive transcription factors and protein kinases for cell survival, proliferation, adaptive homeostasis, and apoptosis, in addition to host defence mechanisms like phagocytosis and microbicidal activities. Apparently, OS elevation seen in pregnancy would cause potential tissue damage (12, 13). Luckily high OS is balanced by the elevation in the production of antioxidants. When the oxidative is superior to the antioxidant defence in the placenta, the oxidative damage might spread to other tissues.

CoV-19 in pregnant women could complicate the outcome of pregnancy as the infection by this virus correlates with OS, a pro-inflammatory state, cytokine production, and cell death. CoV-19 infection is also leads to stimulation of the natural immune system, and it is one of the important effects of CoV-19, as it is accompanied with increased lung destruction and an inert clinical course. As a result, in severe cases of the disease, there is an activation of a large number of neutrophils, macrophages, and mast cells causing a higher release of pro-inflammatory cytokines known as the cytokine storm. This phenomenon can lead to uncontrolled infection, lymphocyte consumption and higher tissue damage. Pregnant women with cytokine storm as a result of CoV-19 infection will have similar clinical pictures and symptoms, similar to non-pregnant counterparts. Since OS and cytokine storm are involved in the CoV-19 pathogenesis, a pregnancy with this disease should be carefully monitored (14).

CoV-19 in pregnant women-clinical presentation and investigations

According to a report by the CDC, common symptoms in patients with CoV-19 in the general population were cough, fever, myalgia, chills, fatigue, headache and dyspnoea. However, fever, cough and generalized weakness were also the important clinical symptoms, found in both: pregnant women and non-pregnant patients with CoV-19. Nevertheless, myalgia and chill were more prominent in pregnancy while dysgeusia and fatigue in non-pregnant patients. Regarding fever and cough, pregnant women with CoV-19 manifested fever with similar odds to non-pregnant women with CoV-19; but less likely to show cough, fatigue, sore throat, headache and diarrhoea. Different studies suggest asymptomatic course of the CoV-19 disease in pregnancy (15).

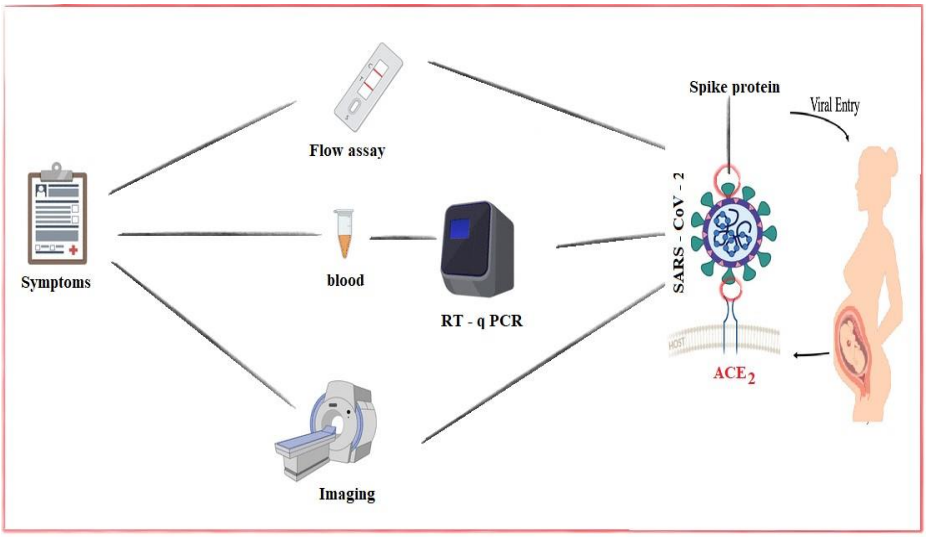

Figure 2. The CoV-19 diagnosis as combination of clinical symptoms, PCR-test, and computed tomography (CT) (*adopted by da Silva et al., 2020 (31)*).

The CoV-19 diagnosis was a combination of clinical symptoms, PCR-test, and computed tomography (CT) (Figure 2). As for the general population, some pregnant patients had a negative PCR-test but clinical symptoms and abnormalities in lung CT-scan, related to CoV-19 (16).

Pregnant women with CoV-19 showed similar imaging lesions vs. non-pregnant patients. In a large group of CoV-19 patients from the general population, the most significant laboratory findings were increased: reactive proteins (CRP), interleukin, erythrocyte sedimentation rate (ESR), lymphopenia and lactate dehydrogenase (LDH); and as second plan decreased: albumin, and eosinophils (15, 16). Leukopenia, lymphopenia, increased LDH, CRP and ferritin were also the most common laboratory findings among CoV-19 patients (17). Compared with non-pregnant patients with CoV-19, pregnant women had similar changes in laboratory values such as altered leucocyte and platelet counts (increased or decreased), elevated CRP and D-dimer. The common laboratory findings in pregnant patients were in turn neutrophilia, lymphopenia and raised CRP (17, 18). Pregnant women had a higher leucocytosis and thrombocytopenia, and lower elevated CRP. D-dimer was elevated in both groups, but higher in pregnancy with lymphopenia and raised CRP. Elevated leucocyte and neutrophil counts were common in pregnant patients compared with non-pregnant adults. In the same study, no significant difference was observed for lymphopenia between groups. Other studies, reported elevated inflammatory markers such as WBC, neutrophil, CRP, procalcitonin and D-dimer were significantly higher in pregnant women, whereas mean lymphocyte percentage was lower than in non-pregnant women (18, 19, 20). Physiologic alterations in laboratory tests during pregnancy may influence the interpretation of the values of pregnant women with CoV-19. Elevated leucocyte counts, particularly neutrophil count, lymphocytopenia and thrombocytopenia are expected changes in pregnant women. Furthermore, CRP values have been shown to be elevated in pregnant women than non-pregnant persons and may further elevate during labour. Co-infection in pregnant women can be the cause of the noticed laboratory changes like elevated leucocytes and CRP.

DISCUSSION

One in three pregnant patients with CoV-19 had pre-existing medical conditions, as diabetes (including gestational and non-gestational) and bacterial co-infection (20, 21). The presence of diabetes, bacterial and viral co-infection was also more common in pregnant women with CoV-19 compared with non-pregnant, CoV-19 women. These findings can be explained by the relative immunosuppression status as a result of pregnancy adding to that the immunocompromised state developing during SARS-CoV-2 infection. On the other side, they may also be related to the unfavorable pregnancy outcomes such as preterm labor and low birthweight. The high maternal BMI and obesity in were higher in pregnant women with SARS-CoV-2. It is believed that obese patients are more possible to admit in the hospital due to obstetric complications. Obesity is a risk factor for different pregnancy complications and maternal death (20, 21). It is also an independent prognostic factor for the severity of CoV-19. A report from the CDC also indicated a high frequency of chronic lung disease, diabetes mellitus and cardiovascular disease among pregnant patients with CoV-19. Regardless of the possible impairment of the immune system in pregnancy, comorbidities likely play a role in the infection and developing complications (20, 21).

The most common obstetric outcomes were postpartum haemorrhage, caesarean delivery, and preterm birth, respectively (22). Compared to women without CoV-19, preterm birth, caesarean delivery and LBW were more probable in women with CoV-19 and low or absent heterogeneity were observed between studies. Higher odds of preterm birth in women with CoV-19 compared to healthy women were reported by other meta-analyses (22). Preterm delivery and birth weight did not show a significant association with CoV-19 in pregnant women, and caesarean delivery occurred in 50% of the patients. Indications for the caesarean section were not clear in most of the reports to show if they were due to medical indications. In this context, a systematic review of the pregnant CoV-19 cases reported a high proportion of preterm births by caesarean delivery (23). Among cases with the available indications for caesarean delivery, the majority were due to CoV-19 pneumonia. Therefore, there is an urgent need to address these issues. Higher proportions of comorbidities in pregnant

patients could have predisposed them to elevated risk for pregnancy complications in addition to a higher risk for incidence and severity of CoV-19. Neonatal intensive care unit (NICU) admission was shown to be higher in neonates of pregnant patients with CoV-19 than neonates born to patients without CoV-19. Some reports showed on/ no evidence of vertical transmission and all samples taken from the neonates like throat swab, amniotic fluid, cord blood and breast milk were negative (24). Real-time polymerase chain reaction (RT-PCR) of nasopharyngeal or anal swabs of infants born to infected mothers was reported. Elevated SARS-CoV-2 IgM and IgG were also observed in the neonates of mothers with CoV-19, while the results of the RT-PCR were negative for SARS-CoV-2 (25). This suggests that elevated anti-SARS-CoV-2 antibody is not a strong evidence for vertical transmission due to the possible transfer from mother to infant. ACE2 is strongly expressed in maternal–fetal interface involving the placenta and decidua (26). Therefore, it can be assumed that the virus can invade and damage the placenta and increase placental permeability. It can lead to placenta insufficiency and some of the obstetric complications that were reported in women with CoV-19 such as abortion, LBW or preterm birth. Based on the suggestive evidence for direct placenta invasion, caesarean delivery may not significantly decrease the risk of vertical transmission. In this regard, the neonates of the mothers with CoV-19 were assessed for having the infection. It was reported that the risk was low and caesarean delivery and breastfeeding did not increase the risk in addition, in most studies, infants with positive test results for SARS-CoV-2 were asymptomatic or developed mild symptoms (27).

It is believed that maternal mortality and morbidity, or what is called '*composite adverse maternal outcome*', that involves at least one of the following: admission to the intensive care unit (ICU), mechanical ventilation use and death. Secondary complications such as miscarriage, stillbirth, neonatal death (23), perinatal death, small-for-gestational age (SGA), preterm birth (28), cesarean delivery, low birth weight, admission to the neonatal ICU (NICU) (29), and vertical transmission confirmed by a positive RT-PCR assay in the neonate **(Table 1).**

Table 1. *Typical secondary complications and details for miscarriage, stillbirth, neonatal death, perinatal death, small-for-gestational age (SGA), preterm birth, cesarean delivery, low birth weight, admission to the neonatal ICU (NICU), and vertical transmission.*

Secondary complications	Details
Miscarriage; Pregnancy loss	<22 weeks' gestation and stillbirth as intrauterine death at or >22 weeks.
Neonatal death	Neonatal death was defined as death of a live born infant within the first 28 days postpartum, and perinatal death as either stillbirth or neonatal death
SGA	SGA was defined as ultrasound estimated fetal weight less than the 10th percentile14.
Preterm birth	Preterm birth was defined as delivery <37 completed weeks of gestation and low birth weight as birth weight less than <2500 g;
Fever	Defined as an axillary temperature of 37.5°C or higher.
Lymphocytopenia	defined as a lymphocyte count <1500 cells/mm^3
thrombocytopenia	platele count <150 000/mm^3
Increased lactate dehydrogenase (LDH) level	higher than 443 U/L in the first trimester, 447 U/L in the second trimester; 524 U/L in the third trimester
computed tomography (CT) scan	Performed at the physicians' discretion. CT abnormalities related to SARS-CoV-2 included 'ground-glass' opacity with or without consolidation or visible intralobular lines.
Acute respiratory distress syndrome (ARDS)	Defined in accordance with the WHO interim guidance 11.
Common criteria for admission to the ICU	included all respiratory arrests, respiratory rate ≥ 40 or ≤ 8 breaths/min, oxygen saturation < 90% on ≥ 50% oxygen, all cardiac arrests, pulse rate < 40 or > 140 beats/min, systolic blood pressure < 90 mmHg, sudden fall in level of consciousness (fall in Glasgow coma score of more than 2 points), repeat or prolonged seizures, rising arterial carbon dioxide tension with respiratory acidosis and any patient giving cause for concern.
Common reasons for admission to the NICU	prematurity, respiratory distress syndrome, sepsis, hypoglycemia and maternal chorioamnionitis

In relation to the effect of SARS-CoV-2 on OS, it was found that there are no significant differences in pregnant women with mild Covid-19 symptoms and asymptomatic pregnant women in comparison to pregnant women with no SARS-CoV-2 infection and this suggest the absence of OS disturbances in Covid-19 pregnant patients. Nevertheless when the all positive SARS-CoV-2 pregnant women whether asymptomatic or symptomatic whether mild or severe the following of oxidative stress showed significant elevation in the level of H_2O_2 production and glutathione (GSH) in infected pregnant women if compared to uninfected pregnant women with CoV-19. This suggests the absence or even reduced oxidative stress in asymptomatic to mild symptom SARS-CoV-2 pregnant patients (30).

CONCLUSION

A total of 30 studies about SARS-CoV-2 during pregnancy and its impact over pregnancy outcomes and OS showed that the antioxidant-prooxidant imbalance in favour of the damaging pro-oxidant condition that can be seen during the cascade of inflammatory reaction noticed during CoV-19 infection and successively in the severity of the disease (15,16). The relationship between inflammation and oxidative stress is mutual as each one of them can induce the other one as a negative vicious circle (19). CoV-19 in pregnant women can complicate the outcome of pregnancy, since the viral infection is associated with oxidative stress, cytokine production, cell death, and a pro-inflammatory status. The infection with CoV-19 will cause stimulation of the natural immune system and hence lung damage and complicated clinical course (14). The increased rate of preterm birth is mainly induced as a result of complications such as pre-eclampsia and/ or pneumonia. Venous thromboembolism and DIC were other complications noticed in pregnant women infected with SARS-CoV-2. Urgent in-depth analysis of the role of CoV-19 infection on early onset preeclampsia (eoPE) and the oxidative stress role in these conditions.

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