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Review Article

COVID-19 and Intrauterine Fetal Death (IUFD): Possible Immunological Causes and Pathologies

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Introduction

COVID-19; The first recognized outbreak in Wuhan, China, December 2019 is considered a global threat (1,2) and its mortality rate according to WHO, ranges from 2-3% (3,4). The pregnant woman and her fetus are more susceptible to the poor outcomes of COVID-19, in which fatality rate may reach more than 35%(5,6). More than 90% of infected pregnant women suffering from pneumonia are susceptible to a miscarriage and other several adverse outcomes (4). *A case report* of intrauterine fetal death (IUFD) that occurred due to multiple organ dysfunction syndrome (MODS) accompanied by acute respiratory distress syndrome (ARDS) (7).

A systemic review of seventeen published studies (8) reported several adverse fetal and neonatal outcomes, including stillbirth (1.2%) and fetal distress (10.7%). Moreover, one pregnant woman with Covid-19 had a stillbirth, delivered by the cesarean section (CS) according to Liu et al.(7). That occurred after she had a fever and a sore throat at the 34th week of gestation. Her condition worsened and needed to be transferred to the intensive care unit (ICU). The only available information about fetal and neonatal results is for women who were infected in their third trimester. It is still unknown whether the infection in the first or second trimester might increase the incidence of fetal and neonatal death(8). We will try to discuss the relation between COVID-19 and IUFD as possible complications via mentioning possible immunological mechanisms and pathologies for that via available data.

Inflammatory Response of COVID-19 Infection

Inflammatory mediators of SARS infection and cytokine storm

COVID-19 in early stages can invade host cells and aggressively replicate without recognition by the innate immunity of the human body cells(9). It is capable of doing this through its ability to abolish type I interferon (T1IFN) expression after the suppression of signal transducers and activators of transcription (STAT) proteins (10,11).

Then, SARS-CoV-2 destroys the infected cells. The replicated virus with intracellular components are liberated into the body circulation, whichin turn stimulating innate immunity. Consequently, that leads to pro-inflammatory cytokine (IL1β, IL-6, TNF-α, etc.) expression, in addition to adaptive immune cells (CD4+ T cell-derived cytokines, CD8+ T cell-

mediated cytotoxicity and B cell) aggregation (12). Coronavirus can escape from immunological attack by stimulation of T-cell apoptosis(13). Pro-inflammatory cytokines and cytokine storm are launched in the lungs leading to hyper-inflammation immunosuppressive state. As, it results in lymphocyte depletion(14,15).

In 2005, a review published by Perlman et al. (16) included studies on animals that were infected with coronavirus species. This study put many hypotheses for hyperinflammatory and immune response dysregulation. One of them, that coronaviruses may attack immune cells directly causing dysregulation of inflammatory mediators and cytokine storm. Multiple studies linked a hyperinflammatory state and significant morbidities(17). Yingzhen et al. collect clinical records of 85 COVID-19 dead cases in two Wuhan hospitals. They reported a significant lymphopenia (77.6%), anemia (48.2%), hypo-albuminemia (78.8%), thrombocytopenia (41.2%), and hypofibrinogenemia (22.4%)(18).

Many clinical studies report the cytokine and chemokine changes during the phase of acute infection, for at least two weeks after the onset. They found that there is a significant elevation in cytokine levels of T-helper-1 cytokine interferon (IFN)-gamma, inflammatory cytokines interleukin (IL)-1, IL-6 and IL-12(19,20).

The aggressive immune reaction is directly responsible for apoptosis, necrosis and significant cell death which is the chiefcause of comorbidities in viral infection (21). COVID-19 dysregulated inflammation and cytokine storm are the leading causes of reported vascular inflammatory lesions through lymphocyte and monocyte infiltration around vessels which lead to vascular wall edema, focal hemorrhage and increased risk of vascular thrombosis complicated by infarction(22-24).

COVID-19 and Thrombosis

Approximately 5–10% of SARS-CoV-2 patients need ICU admission and mechanical ventilation. That is due to progression to serious pneumonia, significant alveolar damage and ARDS with patchy radiological shadowing or ground-glass opacity (25, 26). Severely ill COVID-19 patients are prone to develop not only hypoxia and excessive inflammation, but also frequent thrombotic manifestations such as pulmonary embolism (about 25 % of cases), deep vein thrombosis (DVT), catheter-related thrombosis and arterial thrombosis (27,28). Besides, microvascular thrombosis and capillary leak syndrome affecting the lungs, kidneys, and heart are also reported, potentially complicated by multi-organ failure (MOF)(29).

Although it cannot be fully ruled out that the hemostatic disorders reported in severely COVID-19 patients are direct effects of coronavirus, these disorders may cause through hypoxia coupled with immuno-triggered thrombo-inflammation accompanied by both endotheliopathy and hypercoagulability (30, 31). SARS-COV-2 associated pro-inflammatory cytokines produce an endothelial injury that results in the release of ULVWF (ultra-large von Willebrand factor) involved in 1ry hemostasis and tissue factor (TF) over expression (29,32). Thus, massive quantities of thrombin are produced with a subsequent state of hypercoagulability(33). Overall, decreased blood flow level that induced by hypoxia mediated vasoconstriction and stasis, along with injury of endothelial wall and hypercoagulability which called Virchow's triad supports an increased hazard of thrombosis in severe coronavirus patients (34).

The incidence of venous thrombosis (pulmonary embolism and DVT) is likely to be further increased by the generation of thrombin in large amounts, while arterial thrombosis that leads to strokes may also be supported by increased levels of ULVWF(35). Pulmonary thrombosis is a pathophysiological substratum of COVID-19-associated ARDS. Severely COVID-19 patients with show alterations in the pulmonary vasculature and alveolar tissue associated with platelet / ULVWF-rich strings bound to the damaged endothelium and the intra-alveolar fibrin particles creating localized/disseminated microthrombi (26). The latter is proposed to happen through a local impairment of the fine balance between host fibrinolytic and coagulation pathways in alveolar spaces (29, 36).

COVID-19 with Pregnancy

Maternal outcomes

A case report in 11 April showed a pregnant woman who, unfortunately, did not survive. She was 27 years old, referred to the hospital with respiratory distress, cough, myalgia, and fever for threedays, leucopenia, thrombocytopenia, and lymphopenia. The first chest x-ray described faint patchy opacities in two lungs (37). CT scan described some faint ground glass opacities under pleura with pleural thickening and pleural effusion which may be the cause of clinical deterioration. She was intubated and put under mechanical ventilation. However, the mean between ICU and mechanical ventilation was reported to be 10.5 days(38). She also has shown kidney injury and proteinuria. The patient was expired after multi-organ failure. Her fetus was born with Apgar score of 0 and did not react to neonatal cardiopulmonary resuscitation protocol. The autopsy shows viral pneumonia, and ARDS (hyaline membrane). The histological findings of paraffin-embedded lung tissue showed alveolar spaces with metaplastic changes and proliferation of pneumocytes in focal areas of the hyaline membrane. Nuclear atypia as a viral cytopathic effect was also seen. The inflammatory cells which are detected at the background were macrophages and lymphocytes. This patient was the first report of maternal death positive for COVID-19 associated with intrauterine fetal death (39).

Another study showed the outcome of nine pregnant patients with COVID-19. They had myalgia (33%), cough (44%) ,fever (78%) and dyspnea (11%). Lymphopenia was presented in 56%, positive RT-PCR for SARS-COV2 (100%) and elevated CPR (75%) were observed. No IUFD, maternal mortality, severe neonatal asphyxia or stillbirth were observed. Neonatal outcomes 22% and 14% were low birth weight and preterm respectively(40). Among the nine reported cases, 89% of them had typical signs of viral infection, and only one presented on the right side, patchy consolidation under pleura(41). Another study showed 13 pregnant diagnosed with COVID-19. Their observations showed that 77% had cesarean section dueto several causes including, premature rupture of membrane (10%) and preterm labour (46%) and respiratory distress (30%)(7). We can say that pregnant women suffer from the same symptoms as non-pregnant as fever, cough, myalgia but this may be complicated in pregnant women to IUFD, stillbirth, premature rupture of membrane or death in rare cases after multi-organ failure.

Fetal outcomes

Perinatal COVID-19 infection may have adverse effects on newborns, causing problems such as fetal distress, premature labour, respiratory distress, thrombocytopenia accompanied by abnormal liver function, and even death. However, vertical transmission of COVID-19 is not confirmed yet (42).Fifteen of the 32 women (47 %) affected by COVID-19 were preterm delivered(43). In the study of Chen et al., all nine mothers were delivered electively via cesarean section, two of which were at 36 weeks' gestation, two cases with fetal distress, No fetal death, neonatal death or neonatal asphyxia has been observed (40).

In the study of Zhu et al. reported on ten neonates, six of them were born prematurely; two were small-for-gestational-age (SGA), and six infants have suffered from intrauterine fetal distress. Chest radiography showed abnormalities in 7 neonates at admission, which included infections neonatal respiratory distress syndrome (NRDS) and pneumothorax .In the study of Liu et al., one of ten cases was a stillbirth, and six patients had preterm labour between 32- 36 weeks of gestation. No vertical transmission in all cases is reported (7).

In a case control study, preterm births of mothers with confirmed or suspected COVID19 pneumonia were 23.5% and 21.1% higher than those of the controls (5.8% and 5.0% in the 2020 and 2019 controls). No serious neonatal asphyxia and deaths have occurred in these newborns (37).

COVID-19 induce IUFD

Immunological causes

COVID-19 patients who develop cytokine storm syndrome are at high risk of IUFD. Cytokine storm is characterized by massive cytokine release in an uncontrolled way which leads to multi-organ system failure and ARDS(44). The patients can have ARDS and anaemia, which will decrease the oxygen delivery to the fetus, which will lead to ischemia and maybe death if not corrected. Cytokine storm can cause DIC, which will lead to placental thrombosis and bleeding, which in turn decreases the perfusion to the fetoplacental unit leading to placental insufficiency and IUFD if not corrected rapidly (45).

Severe sepsis can arise from bacterial community-acquired pneumonia-causing severe respiratory failure, which needs mechanical ventilation. The clinical course includes sudden deterioration after 7-8 days after the first symptoms which support the theory which states that this illness is caused by a different immune mechanism that is likely different from sepsis and the low lymphocytic count and liver dysfunction and high D-Dimer supports this theory(46). So, we assume that sepsis may cause intrauterine infection leading to intrauterine death.

A case series of three patients one of them is a 69-year old male with a history of diabetes, hypertension, and stroke presented with symptoms suggestive of SARS-CoV-2 infection which was confirmed with RT-PCR testing and on examination, this patient was found to have bilateral lower extremity ischemia in digit two and three, he did a computed tomography on the brain which showed multiple infarcts and on doing serologic testing he was found to have anticardiolipin IgA antibodies, IgA, IgG antibodies and anti–β2 glycoprotein I . Another two patients with the same finding were found in a COVID 19 specialized ICU in Tongji Hospital ,one of them was a 70-year male with a history of hypertension, emphysema, nasopharyngeal carcinoma and stroke and the other was a 65-year old female patient with a history of hypertension, diabetes, coronary artery disease and no history of thrombosis and their diagnosis with SARS-CoV-2 infection was confirmed with RT-PCR testing(47).

The diagnosis of the antiphospholipid syndrome depends on the presence of these antibodies which can arise transiently in various viral infections (48) and according to these series it can be present in COVID-19 patients and lead to multiple thrombotic complications including placental thrombosis in pregnant women leading to IUFD.

Pathological causes

There are a lot of interesting crossing points between pathological causes that leading to IUFD and the damaging effect of COVID-19 infection. So, we will discuss here COVID-19 infection results in pathology that may cause IUFD in infected pregnant women.

1. Anemia, as there are increasing concerns about Covid-19's causing anaemia based on laboratory evidence of low RBCs count in SARS-Cov2 patients. Some researches explain that by some viral proteins that attach beta-chain of RBCs' HB, that will destroy its capability to transfer oxygen (49). On the other side, anaemia is known to cause low birth weight, premature birth and low Apgar score, which contribute to fetal death(50).

2. Respiratory failure, as a well-established concept. SARS-Cov2 affects the respiratory system primarily. It causes various degrees of pneumonia that results in hypoxemia. On the fetus, hypoxia has a disastrous effect through growth restriction, inflammations, uteroplacental insufficiency and neurological disorders like cerebral palsy, which collectively can cause fetal demise (51).

3. Fetal infections, based on the fact that: Individuals with low immunity are more susceptible to SARS-Cov2 infection and also SARS-Cov2 patients are more susceptible to 2ry bacterial infection, So the occurrence of septicemia in pregnant women is a high possibility, and it will directly affect fetal viability(52).

4. Thromboembolism, as previous studies show that COVID-19 infection is associated with thromboembolic complications that can lead to placental insufficiency and hence fetal mortality(53).

Difficulties in diagnosis

Suspected COVID-19 patients usually present with fever, cough, dyspnea, and other symptoms. Diagnosis cannot depend only on symptoms as they are not specific, variable and the patients can be asymptomatic(54). Some relatively non-frequent symptoms of COVID-19 involved neurologic features such as headache, nausea and vomiting (55). A case report described a 24-year-old male with headache, fatigue and fever who was negative by RT-PCR for the nasopharyngeal swab on the first day while one out of two samples of a CSF was positive for COVID - 19. Another examination was done and the second CSF sample was also positive while the nasopharyngeal swab was still negative or COVID-19(56). As for pregnant women with Covid-19, a study included 60 pregnant women evaluated their clinical course which was similar to those non-pregnant women starting with the common symptoms of fever, cough and dyspnea to the less common fatigue and malaise. The neonates tested negative for the virus (57).

Other studies also supported that pregnant women have the same clinical course as non-pregnant women (38,58). Since the symptoms are non-specific, it is better looking for the diagnosis using diagnostic tests such as PCR andchest CT scans (59–61). Although PCR is the gold standard for diagnosis (62), there are some disadvantages including lack of PCR reagent kits, the unavailability of PCR in rural areas and PCR is useless in detecting the previous infection if the patient recovered from COVID-19 (63). A case report also mentioned that after four negative nasopharyngeal swabs, PCR test came positiveon the fifth time, while the early CT scan showed abnormalities indicating COVID-19 infection. This emphasized the use of CT scan in diagnosis when PCR cannot detect the viruses at an early stage (64–66). Considering the lack of kits and the high rate of false-negative PCR test, CT was added to support COVID-19 diagnosis based on abnormalities in the images as mainly ground-glass opacities in both lungs (67,68). However, features of lung radiology differ according to the phase and onset of the disease. Also, CT has low specificity and a relatively expensive test (66).

Other tests are being studied as detecting viral antigens and antibodies resulting from the infection in the patient's serum, but the viral load may vary during the disease and decreasing the efficacy of detection (69). Nucleic acid detection techniques are under development, such as isothermal amplification (70). Point of care and smartphone surveillance use is also on the rise (63). Although CT scan is the standard for lung imaging abnormalities, lung ultrasound is suggested by the Chinese critical care study group as an alternative for CT, especially for pregnant women (71).

Conclusions

It is still unknown whether the infection in the first or second trimester might increase the possibility of fetal and neonatal death. Future researches following and discussing those long term outcomes is needed.

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