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The association between preeclampsia and COVID-19; a narrative review on recent findings

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease first diagnosed in December 2019. Regarding previous studies that indicated the potential association between preeclampsia (PE) and COVID-19, it is pertinent to assess these conditions' clinical manifestations and laboratory findings comprehensively. We performed this narrative review, considering the importance of pregnancy and its maternal and fetal outcomes and the lack of a definite mechanism of COVID-19 in pregnant women with PE. It is noteworthy that both conditions may have overlapped characteristics that may affect the outcomes during pregnancy.

Keywords: Coronavirus, COVID-19, COVID-19 vaccines, Hypertension, Preeclampsia, Pregnancy

Implication for health policy/practice/research/medical education:

Regarding the outbreak of coronavirus disease 2019 (COVID-19), analysis of the interrelationship between the clinical manifestations and laboratory findings of preeclampsia and COVID-19 would be necessary.

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Introduction

Coronavirus disease 2019 (COVID-19), which occurs due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first diagnosed in December 2019, and was declared a pandemic in March 2020. It causes infections ranging from a flu-like syndrome to severe health-related problems. Although the respiratory system is the primary site of infection, it can affect the liver and kidneys and cause hypertension. This disease has been associated with the immune system activation and leads to increased proinflammatory cytokines such as interleukin 2 (IL-2), IL-6, IL-7, and tumor necrosis factor- α (TNF- α) (1).

As a result, people with weak immune systems, such as women during pregnancy, elderlies, and patients with other comorbidities, are likely to be highly affected by COVID-19 (2). Generally, a higher risk of infection occurs in pregnant women because they are more vulnerable to viral infection due to their considerable physiological and immunological changes during this sensitive period

of their lives. Thus, there is a major concern about the elevated risk of COVID-19 during pregnancy. As reports indicate, more severe COVID-19 can be expected in these groups (3).

In women, severe COVID-19 can also increase adverse pregnancy outcomes and increase the rate of preterm delivery, cesarean section, preeclampsia (PE), eclampsia, and perinatal mortality (4). A previous study reported histopathological changes in the placenta and poor maternal vascular perfusion in pregnant women with severe COVID-19 compared with the control group (5).

To the best of our knowledge, this virus enters body organs via the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in the cytotrophoblast of the placenta. It affects the proliferation of the trophoblast and angiogenesis during pregnancy and regulates arterial blood pressure (BP) (4).

In addition, PE and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome in the placenta can be occurred due to the effect of COVID-19 on the

downregulation of ACE2. Moreover, it may induce placental oxidative stress, reduce the proangiogenic factors, and affect the release of antiangiogenic factors.

Preeclampsia, with the manifestations of increased BP and proteinuria, is the leading cause of prenatal and maternal morbidity and mortality. It commonly occurs after 20 weeks of gestation, which rapidly progresses (6).

Although some previous studies on infected pregnant women reported a significant association between COVID-19 and an elevated hazard of PE and PE-like syndrome (7,8), others reported controversial results (9,10).

Considering the significance of pregnancy and its outcomes, the importance of assessing the COVID-19 outbreak, and the absence of a definitive mechanism to understand how this virus functions in pregnant women with PE, we conducted this review to carry out a comprehensive assessment of the relationship between PE and COVID-19.

Methods

In this narrative review, we assessed the potential association between PE and COVID-19. To this aim, we used specific keywords such as preeclampsia, COVID-19, pregnancy and fetus to search and extract relative English articles from the Web of Science, PubMed, and Google Scholar. Moreover, we attempted to describe the COVID-19 and its effects on pregnancy, especially PE.

Introducing the recent pandemic (COVID-19)

An outbreak of an atypical form of pneumonia was announced in China in December 2019. In the following months, this pneumonia, entitled “COVID-19,” spread rapidly to other provinces and countries such as Thailand, Korea, and Japan. Therefore, the initial continent where the outbreak started was Asia, due to China having the most COVID-19 cases and deaths.

It has been estimated that approximately 80% of infected patients had the mild-to-moderate form of this virus. Symptoms that commonly occur approximately one week after exposure are as follows:

- Respiratory symptoms: shortness of breath, cough, and sputum
- Musculoskeletal symptoms: fatigue, joint pain, myalgia, and headache
- Enteric symptoms: vomiting, diarrhea, and abdominal pain (11).

The consequences of COVID-19 on women during pregnancy

Despite insufficient evidence on immunological responses to COVID-19 during pregnancy, data from previous pandemics suggest an increased infection and mortality rate in pregnant women compared to non-pregnant women. Gestational age and time of infection may be important factors in differentiating immune responses and outcomes.

Since the 1st and 3rd trimesters are the proinflammatory phases of gestation to facilitate implantation and labor, respectively, infection with COVID-19 in these trimesters puts women at an increased risk of mounting an amplified immune-mediated response against the virus by what can be described as a cytokine storm. Moreover, during labor, the increased inflammation and stress levels may lead to poor outcomes and increase the likelihood of postpartum hospital admission (12).

Preeclampsia is a common complication during pregnancy, which potentially seems to exacerbate COVID-19. A recent international multicenter study on the pregnancy outcomes of 706 women infected with COVID-19 and 1424 women without COVID-19 noted a higher incidence of PE, eclampsia, and HELLP syndrome associated with the infection of COVID-19 during pregnancy (13). Furthermore, it is not easy to distinguish the diagnosis of Preeclampsia from COVID-19 due to their similar abnormalities in laboratory tests. It is notable that abnormal liver function tests and thrombocytopenia are the two diagnostic laboratory tests used to diagnose PE, which may also occur in patients with COVID-19 (14).

Definition and pathophysiology of PE

Preeclampsia is defined as new-onset end-organ damage with proteinuria and hypertension, which occurs after 20 weeks of gestation. Although the exact pathophysiology of preeclampsia is still unknown, several theories have been suggested, with abnormal placentation being the wider-accepted theory. The clinical course starts with an abnormal trophoblastic infiltration, which occurs long before the emergence of clinical symptoms of the illness and sometimes even before knowledge of pregnancy. In proper implantation, trophoblasts infiltrate the decidualized endometrium, causing the remodeling of the spiral arteries and obliteration of the tunica media of the myometrial spiral arteries and facilitating the increased blood circulation to the placenta; all without the intervention of maternal vasomotor alterations. In PE, trophoblasts that fail to acquire an endothelial phenotype cause trophoblast infiltration to be hindered and, consequently, the remodeling of the spiral arteries to be inadequate (15).

Immunological factors, inflammation, infection, and genetic predispositions are some other factors that contribute to this disease manifestation. Lastly, placental hypoxia and ischemia are other influential factors in the pathogenesis of PE, which leads to the signs and symptoms of PE due to the release of vasoactive agents into the maternal bloodstream and the concomitant endothelial cell dysfunction (16).

Prevalence of preeclampsia

Hypertensive disorders (during pregnancy) affect 10% of all pregnancies. As a pregnancy complication characterized

by increased BP and damage to other organs, PE affects 5% to 7% of women during pregnancy and has approximately 70,000-500,000 maternal and fetal mortality rates, and gives rise to the highest annual morbidity and mortality rates. It is a significant cause of maternal mortality, severe maternal morbidity, maternal critical care hospitalizations, cesarean section and preterm births in the United States. Hypertensive disorders during pregnancy have become more common in developed countries. A greater death rate has been reported in African-American women compared with Hispanic, American-Indian, Pacific Islanders, and Asian women (17).

The categorization of preeclampsia

After categorizing hypertension and PE in 1972 by the American Congress of Gynecologists and Obstetricians (ACOG), the modified 2013 version classified them into four groups: chronic hypertension, eclampsia and PE, gestational hypertension and chronic hypertension with PE.

According to this classification, severe PE is described in the case of the existence of one of the following criteria:

1. A BP of more than or equal to 160/110 mm Hg in two separate times
2. Less than 100 000 platelet counts per microliter
3. Impaired liver function: epigastric pain, abnormally increased level of liver enzymes, epigastric or severe and persistent pain in the liver
4. Renal failure; more than 1.1 mg/dL serum creatinine level
5. Doubled serum creatinine level and the presence of pulmonary edema (18).

The Influence of PE on mothers and fetuses during pregnancy

Preeclampsia can affect both the mother and the fetus. Maternal risks include higher rates of hypertension, an elevated mortality rate due to cardiovascular diseases and severe cardiovascular events and an increase in the risk of stroke. Moreover, placental abruption, premature delivery, oligohydramnios, fetal discomfort, placental abruption, intrauterine growth restriction, fetal discomfort, and mortality in pregnancy are the prenatal risks to the fetus (19).

The relationship between COVID-19 and PE

We have to view the potential association between these two conditions from different perspectives. First, we must know that this virus can show similar signs and symptoms to PE. On the other hand, COVID-19 can provide the etiologic path toward PE, or PE forms an environment that raises the risk of COVID-19. Although the higher risk of COVID-19 in pregnant women is unclear, there are similar risk factors for developing severe types of COVID-19 in all women regardless of their pregnancy status, including ethnicity and other comorbidities.

Regarding the potential overlap between risk factors of PE and severe COVID-19, it would be wise to consider this association as a confounding issue (20).

A multinational investigation to assess the associations and symptoms of COVID-19 during pregnancy revealed that pregnant women who were diagnosed with this virus had considerably higher severe pregnancy complications, such as eclampsia and PE, compared with women without a diagnosis of this virus. This virus may be lethal during pregnancy when ICU services are not fully accessible, and a higher maternal mortality rate was noted in these women (13).

Furthermore, it has been estimated that the diagnosis of this virus in women who were already at high risk of PE and COVID-19 (due to comorbidities such as diabetes, hypertension, cardiovascular disease, chronic respiratory diseases and being overweight) induced a 4-fold increased risk of eclampsia and PE. This increased risk could reveal the well-known relationship between these underlying diseases and the acute kidney damage in COVID-19 (20). Additionally, it was found that this infection during pregnancy was related to higher postpartum mortality and morbidity rates in parents and their newborns compared to their uninfected counterparts, especially in the case of symptomatically infected women (13). As COVID-19 and PE appear to have elevated thrombocytopenia, liver enzymes, proteinuria, and raised proinflammatory biomarkers, the diagnosing of PE may become more challenging (2).

Preeclampsia-like syndrome

Studies have shown that several disorders mimic PE and lead to PE-like syndrome. Pathophysiological causes of PE-like syndrome include vasospasm, activation or destruction of platelets, endothelial cell dysfunction and decreased perfusion. One of the most significant challenges for health care providers in the differential diagnosis is the potential overlap in their diagnosis. In addition, some of these disorders have life-threatening potentials for mothers and fetuses. Therefore, an appropriate diagnosis is essential as various options are available for the management and prognosis of these disorders. Notably, the development of PE-like syndrome has been noted in pregnant women with severe COVID-19 (21).

In addition, angiogenic factors can help clinicians differentiate between these disorders and PE. Placental-associated angiogenic factors such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) are highly specific for placental insufficiency. In PE, the placenta cannot properly manipulate and regenerate mothers' uterine spiral arteries, which leads to impaired perfusion and placental oxidative stress. At least five weeks before the onset of clinical PE, the detection of an sFlt-1/PlGF imbalance in mothers' blood circulation is possible (22).

Therefore, patients with COVID-19 with early primary

placental implantation have normal levels of sFlt-1/PlGF despite protein in the urine, decreased platelet count, increased liver enzymes, or high BP. As a result, in some pregnant women with severe COVID-19, sFlt-1/PlGF, and Lactate Dehydrogenase levels can distinguish PE from the PE-like syndrome (21).

Effect of PE and COVID-19 on the outcomes

Some research assessed the potential connection between COVID-19 and PE to identify crucial pregnancy outcomes, such as morbidity and mortality, in maternal and neonatal populations. One large study focused on the impact of this virus on maternal and fetal outcomes during pregnancy. They compared the results for women with COVID-19, PE, both PE and COVID-19, and none of them. In their results, they mentioned that COVID-19 was substantially related to PE, and this relationship existed regardless of risk factors or pre-existing conditions. Although the severity of this virus did not appear to have a significant role in this association, both (either individually or in combination) were associated with preterm delivery, high prenatal morbidity and mortality, and poor maternal outcomes. They noted that in assessing the risk of COVID-19, women with PE should be included in the susceptible category (23).

COVID-19 vaccination and PE

CDC has noted the positive effects of receiving a coronavirus vaccine during pregnancy and recommended vaccination for pregnant women and those trying to conceive in the future. Moreover, previous studies revealed that COVID-19 vaccinations promote immunogenicity against coronavirus infection during pregnancy the same way it does in non-pregnant women. Previous research has found that COVID-19 immunization in pregnant women did not cause significant vaccine-related side effects or adverse obstetric, neonatal, or fetal outcomes (24).

According to a meta-analysis, which included 7670 vaccinated pregnant women and 9392 unvaccinated ones who were assessed for the risk of PE up to 72 hours after delivery, COVID-19 immunization had no negative impacts on the pregnancy, neonatal, or fetal outcomes (25).

Conclusion

Based on the previous studies that indicated the potential association between PE and COVID-19, it seems that considering clinical manifestations and laboratory findings of these conditions is essential. It is noteworthy that these studies may have overlapped characteristics that are likely to affect maternal and fetal outcomes during pregnancy.

Authors' contribution

Conceptualization: AHR, SGHT and AFY. Methodology: AHR, SGHT and AFY. Validation: AHR, GCHN, SGHT

and AFY. Formal Analysis: AHR, GCHN, SGHT and AFY. Investigation: AHR, GCHN, SGHT and AFY. Resources: AHR, GCHN, SGHT and AFY. Data Curation: AHR, GCHN, SGHT and AFY. Writing—Original Draft Preparation: AHR, GCHN, SGHT and AFY. Writing—Review and Editing: AHR, GCHN, SGHT and AFY. Visualization: AHR, GCHN, SGHT and AFY. Supervision: AHR, GCHN, SGHT and AFY. Project Administration: AHR, SGHT and AFY.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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