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COVID-19 AND PREECLAMPSIA: ENDOTHELIAL DYSFUNCTION AS A COMMON PATHOPHYSIOLOGICAL LINK

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Resume. This article presents the results of literary review dedicated to the problem of preeclampsia during COVID-19 pandemics, focusing on endothelial dysfunction as a common pathophysiological link.

Keywords: COVID-19, preeclampsia, endothelium, dysfunction.

Introduction. Preeclampsia is a pregnancy-specific hypertensive disorder defined by the International Society for the Study of Hypertension in Pregnancy as the manifestation of arterial hypertension and proteinuria (300mg/day), occurring after 20 weeks of gestation or as new onset of arterial hypertension combined with organ dysfunctions like renal failure, liver dysfunction, hematological or neurological abnormalities, intrauterine growth restriction or uteroplacental insufficiency. According to the results of the INTERCOVID cohort study, women with COVID-19 were at increased risk of preeclampsia, eclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome (8.4% vs 4.4%; relative risk (RR), 1.76; 95% CI, 1.27–2.43) [1].

Women with either asymptomatic or symptomatic SARS-CoV-2 infection who had risk factors for preeclampsia, such as increased body mass index (BMI), diabetes, pre-existing hypertension, or other chronic comorbidities, were found to have a 4 times greater risk of developing preeclampsia or eclampsia compared with women who did not have SARS-CoV-2 infection. Women diagnosed with COVID-19 were also at increased risk of preterm birth (RR, 1.59; 95% CI, 1.30–1.94). The majority (83%) of preterm births in women diagnosed with COVID-19 were medically indicated; the leading indication was preeclampsia/eclampsia/HELLP syndrome (24.7%)

Aim: to analyze possible pathogenetic links between COVID-19 and preeclampsia/eclampsia in pregnant women.

Material and methods. Most recent scientific articles illustrating the problem of hypertensive disorders in pregnant women during COVID-19 pandemics were analyzed. The search included PubMed database, Cochrane database, and Scopus database of scientific journals.

Results and their discussion. Maternal deaths examined in SARS Cov-2 positive antenatal women showed an increase AST, ALT, total bilirubin, cardiac enzymes, serum creatinine and urea, which were, basically, quite similar to the enzymatic changes that occur in preeclamptic patients.

On analyzing possible mechanisms of endothelial damage, it was established that ACE-2 has varying localization and is a functional receptor of SARS CoV-2; increased serum and placental levels of pro-inflammatory cytokines and decrease of anti-inflammatory cytokines are seen in both pathologies; presence of 3 common factors of endothelial damage was described, such as NETosis, anti-phospholipid antibodies (aPLAs) & alpha-1 antitrypsin.

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NETosis (Neutrophil Extracellular Traps) bind to Von Willebrand Factor and recruit platelets, trigger platelet activation, bind to TF and stimulate extrinsic pathway activation and thrombin generation, support Factor XII activation mediated by platelet derived polyphosphates. This contributes to preeclampsia development by being associated with maternal vasculitis, maternal fetal interface hemorrhage and laminar decidual necrosis and also COVID-19 related endothelial damage & immune-thrombosis via platelet neutrophil interaction [2].

Anti-phospholipid antibodies (aPLAs) are an important risk factor for Early Onset of Preeclampsia (EOPE). At the same time, a recent study reported a 52% increase in aPLAs levels in COVID-19 patients [3]. In placenta they promote platelet & EC activation which directly induces procoagulant activity by interacting with the factors of coagulation pathway.

Anti-beta 2 glycoprotein-I is a primary pathogenic antibody in antiphospholipid syndrome, amplifying production of other mediators of effector cell activation including C3a, C5a and MAC resulting in thrombosis, tissue hypoxia and inflammation within the placenta.

A genetic susceptibility has been observed in dysregulation of C activation in pregnant women with PE/HELLP syndrome and in patients with COVID-19 leading to its moderate/severe progression.

Of the 28 studies included in the systematic review and meta-analysis by Conde-Agudelo and Romero, 14 were conducted in North America, six in Europe, five in Asia and two in Latin America. The UK study, which included white (76.3%), Asian (12.2%) and black (4.6%) pregnant women, found that the association between SARS-CoV-2 and preeclampsia persisted even after multiple regression adjusting for maternal age, ethnicity, parity, pre-existing diabetes mellitus, pre-existing hypertension and socioeconomic deprivation measured using the index of multiple deprivation 2019

The INTERCOVID study found that women who were overweight at the first antenatal visit and who were subsequently diagnosed with COVID-19 had the highest risk of preeclampsia/eclampsia (RR, 2.62; 95% CI, 1.57–4.36), which suggests that being overweight modifies the effect of COVID-19 exposure.

Biological gradient (dose-response relationship): In the systematic review by Conde-Agudelo and Romero, both asymptomatic and symptomatic SARS-CoV-2 infection significantly increased the odds of preeclampsia. However, the association was stronger in patients with symptomatic infection (OR, 2.11; 95% CI, 1.59–2.81) than in those with asymptomatic infection (OR, 1.59; 95% CI, 1.21–2.10). The INTERCOVID study reported that longer duration of symptomatic COVID-19 was associated with an increased RR of preeclampsia, eclampsia or HELLP syndrome.

Several mechanisms have been proposed by which SARS-CoV-2 infection might cause systemic complications, such as high blood pressure, liver injury and thrombocytopenia, as well as the respiratory disease typical of COVID-19. One theory proposes involvement of the angiotensin-converting enzyme 2 (ACE2) receptor.

Laboratory evidence that demonstrates downregulation of ACE2 and increased production of antiangiogenic factors, nitric oxide modulators and prothrombotic molecules as

a result of SARS-CoV-2 infection is consistent with the epidemiological data. Some histopathological studies have also identified placental lesions in COVID-19. When compared with controls, placentae of women with severe COVID-19 showed histopathological changes associated with poor maternal vascular perfusion. This included decidual arteriopathy, peripheral and central villous infarction and villous agglutination. The placenta of a patient with symptomatic COVID-19 at the time of delivery was found to have prominent lympho-histiocytic villitis and was one of two placentae that showed maternal malperfusion changes. This may indicate that placental changes are most likely to occur during the acute phase of the disease.

The concept of reversibility suggests that if SARS-CoV-2 infection can cause preeclampsia, then vaccination against COVID-19, antiviral therapies and COVID-19 pandemic mitigation measures would be expected to reduce the risk of preeclampsia. In a study that compared pregnancy outcome between women who were vaccinated and those who were unvaccinated against COVID-19, vaccination was found to protect against SARS-CoV-2 infection prior to delivery (1.4% vs 11.3%; RR, 0.13; 95% CI, 0.03–0.50; P = 0.003) and was also associated with a non-significant decrease in the incidence of preeclampsia (0.7% vs 1.2%; RR, 0.58; 95% CI, 0.08–4.25; P = 0.59).

On analyzing different aspect of Bradford Hill criteria in association with potential link between COVID-19 & Preeclampsia, it can be deduced that there is growing evidence that the association between SARS-CoV-2 infection in pregnancy and preeclampsia is causal, particularly in relation to the biological gradient and plausibility. Clearly, however, more evidence is needed to bolster the other criteria, particularly in relation to temporal sequence, which is perhaps the only criterion which epidemiologists universally agree is essential to causal inference [4]. It is possible that a causal link is mediated through placental or cardiovascular pathology, but further studies are required to understand these potential mechanisms. But healthcare professionals should be aware that SARS-CoV-2 infection in pregnant women despite being asymptomatic pose a threat for development of preeclampsia and those who test positive for SARS-CoV-2; their blood pressure, liver & renal function should be monitored to prevent the onset of preeclampsia and HELLP syndrome [5].

Quite interestingly, there are debates on a potential role of neurofilament in COVID-19 and preeclampsia. According to scientists, neurological markers of COVID-19 have been observed in patients, such as mild to severe headaches, cognitive impairment, fogginess, rarely Guillain-Barre syndrome (GBS) etc. In CSF & blood, neurological dysfunction biomarkers like serum neurofilament light (sNFL) have been associated with severe COVID-19. Axonal lesions or injury causes release of neurofilaments (intermediate filaments nestin) which is also important for maintaining the integrity of axons into the CSF & blood that are noted as important Biomarkers of COVID-19. A study showed that plasma NFL levels were 3.1 times higher in 18 patients who developed severe COVID-19 compared to healthy age-matched SARS-CoV-2-negative individuals. At the same time, there also is a link between neurofilament and preeclampsia: sNFL has previously been reported as a serum marker predicting preeclampsia with an accuracy similar to that of the more established angiogenic factor markers, soluble fms-like tyrosine kinase-1 (sFlt-1)

and placental growth factor (PlGF); levels of sNFL increased with maternal age (> 36 years), with a greater increase in women with preeclampsia compared to controls. In another study, women with preeclampsia without clinically detectable neurological complications had increased CSF and plasma concentrations of NFL compared to women with normotensive pregnancies.

Conclusions:

1. COVID-19 pandemics poses a serious problem for pregnant women, significantly increasing the risk of hypertensive disorders, such as gestational hypertension, preeclampsia and eclampsia.

2. COVID-19 and preeclampsia share common pathophysiological mechanisms, explained mostly be endothelial damage, and also by neurofilament theory.

3. Vaccination against COVID-19, antiviral therapies and COVID-19 pandemic mitigation measures are expected to reduce the risk of preeclampsia, therefore, vaccination should be promoted as an essential preventive measure, especially in fertile women that are planning to conceive.

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