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LETTER TO THE EDITOR

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COVID-19: A new risk factor or just a new imitator of preeclampsia? NLRP3 activation: A possible common mechanism

Dear Editor,

We read an article in the Journal of Medical Virology entitled "Being pregnant in the COVID-19 pandemic: Effects on the placenta in all aspects"[1] that focused on revealing the effects of the virus on the placenta in all aspects. We would like to contribute with findings regarding the interplay among inflammation caused by SARS-Cov-2 infection in placenta with Nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, as a possible common mechanism in placenta from pregnancies complicated by preeclampsia.

It has been recognized that pregnant women constitute a special vulnerable group for complications related to the COVID-19.[2] It is possible to speculate that physiological changes observed throughout pregnancy, such as an increase in circulatory volume, pulmonary congestion, and fluctuation between Th1 and Th2 responses may contribute to the pregnancy susceptibility to respiratory virus diseases. Additionally, the COVID-19 syndrome has been associated with higher rates of adverse pregnancy outcomes such as miscarriage, preterm birth, fetal growth restriction, perinatal death, and mainly preeclampsia.[3]

In fact, the intriguing pathophysiology of SARS-CoV-2 infection shares many characteristics with preeclampsia, mainly regarding the great inflammatory biomarkers release.[4] This common interface may put COVID-19 as a new imitator of preeclampsia. However, specific common immunological mechanisms between these severe diseases have not yet been described. Here, we speculate a possible common involvement of NLRP3, and consequent inflammatory cytokine storm in COVID-19 and preeclampsia.[5]

Inflammasomes are activated by endogenous danger/damage-associated molecular patterns (DAMPs) and exogenous pathogen associated molecular patterns.[6] The NLRP3 inflammasome has an apoptosis-associated speck-like protein with a caspase recruitment domain (ASC), and caspase-1 as an interleukin (IL)-1β-converting enzyme. Activated caspase-1 cleaves the precursor cytokines pro-IL-1β and pro-IL-18, generating the strong inflammatory cytokines IL-1β and IL-18, respectively.

The coronavirus SARS-CoV-2 leads to direct activation of NLRP3 by a viral protein, named viroporin protein 3a.[5] This viral protein is present on the genome of SARS-CoV-2 suggesting that this virus can also directly activate NLRP3. This activation has been strongly correlated to the inflammatory response seen in some patients with COVID-19.

Preeclampsia is a placental-mediated disease.[6] Oxidative stress has been described as an important pathway of syncytiotrophoblast damage and this damaged tissue produces abnormal amounts of debris and necrotic particles which are rich in exosomes, microRNAs, and antiangiogenic factors.[7] All these products are launched into the maternal circulation and cause a systemic inflammatory response and endothelial dysfunction. Weel et al.[8] demonstrated a significantly higher expression of NLRP3 and caspase-1, IL-1β, and IL-18 in placental samples from women with preeclampsia compared to normotensive pregnant women. Our group demonstrated that oxidative stress induction of placental explants acts as a DAMP and leads to NLRP3 activation.[9] We also demonstrated that after this initial placental NLRP3 activation, peripheral maternal innate immune cells also express NLPR3 activation, mainly among women with severe preeclampsia.[10]

The clinical presentations of both COVID-19 and preeclampsia are diverse. Both diseases can lead to mild or extremely severe clinical forms, characterizing different phenotypes. van Der Berg & Velde[5] suggested that different intrinsic immune capacities can determine different degrees of NLRP3 inflammasome activation and these different responses may contribute to the diverse clinical scenarios seen in COVID-19. Similar process has been described in pregnancy once a controlled inflammation is essential for pregnancy implantation, host defense, and parturition. However, excessive inflammatory responses are correlated with several pregnancy adverse outcomes, mainly preeclampsia.[11]

The role of COVID-19 as a risk factor for preeclampsia is still controversial. The main reports have pointed out that preeclampsia is associated with severe cases of COVID-19, but is not present in mild or moderate cases of the disease[12] It is important to consider that these patients with phenotypes of COVID-19 and preeclampsia share common risk factors, such as obesity, chronic arterial hypertension, diabetes and other metabolic diseases. Bearing in mind the current analyses, it is only possible to speculate that COVID-19 and preeclampsia have common pathophysiological mechanisms such as NLRP3 activation that act in synergism for a final clinical manifestation. Therefore, inhibitors of NLRP3 could be a very effective treatment for PE. Meanwhile, the interactions between

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NLRP3 inflammasome-regulated pathways may improve the treatments of inflammation-related disorders, such as PE and COVID-19.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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