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HISTOPATHOLOGICAL CHANGES IN PLACENTALS IN INTERCURRENT PREGNANCY: FOCUS ON COVID-19 AND PREECLAMPSIA

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Abstract: The placenta is a highly specialized organ responsible for transporting nutrients and metabolic waste from the mother to the fetus. Adequate placentation is essential for normal embryonic development and poor placental development is associated with several complications of pregnancy, such as preeclampsia. In addition, the pandemic caused by the new acute respiratory syndrome coronavirus 2 (SARS-CoV-2), demonstrated a strong relationship with the risk of miscarriage, increased incidence of preeclampsia, stillbirths and prematurity. The role of COVID-19 as a risk factor for preeclampsia is still controversial. The main reports point out that preeclampsia is associated with severe cases of COVID-19, but is not present in mild or moderate cases of the disease. Future studies are needed to collect more robust data to further validate or substantiate these findings, better understand the pathophysiological pathways that explain these associations, and identify effective strategies to prevent adverse outcomes in pregnant women with COVID-19.
Keywords: Placenta; Placentation; Placental diseases; Placental circulation.

INTRODUCTION

The placenta is a highly specialized organ, essential for fetal life [1,] as it is responsible for transporting nutrients and metabolic waste from the mother to the fetus [1,2.] The placenta is developed through the fusion of fetal membranes with the uterine mucosa, being formed by a fetal and a maternal component [3.] Chorionic villi are the main fetal component of the placenta and consist of matrix with mesenchymal nucleus, fetal cells and blood vessels, while the maternal components are intervillous blood and decidua basalis, which contain decidualized endometrial cells and immune cells such as macrophages and lymphocytes. [4]

Pregnancy begins with the implantation of the embryo, which adheres to the wall of the uterus. The implanted embryo is composed of an inner cell mass that develops into a fetus and an outer trophoblastic layer that forms the placenta. The trophoblastic layer differentiates into cytotrophoblast and syncytiotrophoblast, forming the villous structure. The cytotrophoblast invades the maternal tissue and allows the vascularization of the trophoblast in order to establish and maintain the fetoplacental vasculature [1.]

At the end of the first trimester of pregnancy, the primitive placenta undergoes remodeling and gives rise to the definitive organ, a process associated with the beginning of maternal arterial circulation, mediated by oxidative stress and increased oxygen concentration. The beginning and subsequent development of the uteroplacental circulation depend on the conversion of highly contractile endometrial spiral arteries into dilated and flaccid vessels [3.]

Adequate placentation is essential for normal embryonic development [1] and poor placental development is associated with several complications of pregnancy, such as preeclampsia [1.] Preeclampsia is a disorder resulting from endothelial damage and an antiangiogenic state [5,] responsible for the emergence of hypertension above 20 weeks of gestational age, associated with the emergence of new proteinuria or hepatic, renal, neurological, hematological or uteroplacental dysfunction. In addition, it is associated with fetal growth restriction, higher fetal mortality, prematurity and neonatal respiratory syndromes [6.] The pandemic caused by the new acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown a strong relationship with an increase in the incidence of preeclampsia [5,] risk of miscarriage, stillbirths and prematurity [7,] occasion in which delivery occurs before 37 weeks of gestation [8.] Therefore, the histopathological examination

of the placental tissue can contribute with significant information about maternal-fetal health.[7]

JUSTIFICATION

Gestational complications, such as preeclampsia and, currently, COVID-19, in addition to being very prevalent when evaluating obstetric patients, are responsible for several consequences for the maternal-fetal binomial, such as increased morbidity and mortality. Therefore, the histopathological evaluation of placentas after gestational complications is important, so that the mechanisms of maternal-fetal suffering can be better understood and prophylactic and therapeutic measures can be carried out, in an attempt to reduce maternal-fetal morbidity and mortality caused by such disturbances.

MATERIAL AND METHODS

It was also hoped that this study could contribute to making the development and implementation as successful as possible. Therefore, the objective of this study was to use the action research methodology to introduce, study and clarify the relationship between the repercussion in patients with chronic kidney diseases and the use of non-steroidal anti-inflammatory drugs in different contexts, in order to meet to the local needs of specific patients.

RESULTS

From the analysis of the article in the Journal of Medical Virology titled "Being Pregnant in the COVID-19 Pandemic: Effects on Placenta in All Aspects"9 that focused on revealing the effects of the virus on the placenta in all aspects. We would like to contribute to the findings on the interaction between inflammation caused by SARS-Cov-2 infection in the placenta with the pyrin domain of the Nod-like receptor family containing inflammasome 3 (NLRP3) activation, as a possible common mechanism in placenta of pregnancies complicated by preeclampsia.

It has been recognized that pregnant women constitute an especially vulnerable group for complications related to COVID-19 10. It is possible to speculate that physiological changes observed throughout pregnancy, such as increased circulatory volume, pulmonary congestion, and fluctuation between Th1 and Th2 responses, may contribute to the susceptibility of pregnancy to respiratory viral diseases. In addition, COVID-19 syndrome has been associated with higher rates of adverse pregnancy outcomes such as miscarriage, preterm birth, fetal growth restriction, perinatal death, and especially preeclampsia.[11]

In fact, the intriguing pathophysiology of SARS-CoV-2 infection shares many characteristics with preeclampsia, particularly with regard to the release of major inflammatory biomarkers 12. This common interface may place COVID-19 as a new mimic of the disease. However, common immunological mechanisms specific among these serious 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.[13]

Inflammasomes are activated by endogenous danger/damage-associated molecular patterns (DAMPs) and exogenous pathogen-associated molecular patterns 14. 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 pro-IL-1β and pro-IL-18 precursor cytokines, generating the strong inflammatory cytokines IL-1β and IL-18, respectively.

The SARS-CoV-2 coronavirus leads to the direct activation of NLRP3 by a viral protein, called viroporin protein 3[a] 15. This viral protein is present in the genome of SARS-CoV-2 suggesting that this virus can also directly activate NLRP3. This activation was strongly correlated with the inflammatory response seen in some COVID-19 patients.

Preeclampsia is a disease mediated by the placenta 16. Oxidative stress has been described as an important pathway of damage to the syncytiotrophoblast and this damaged tissue produces abnormal amounts of debris and necrotic particles rich in exosomes, microRNAs and antiangiogenic factors 17. All these products are released into the maternal circulation and cause a systemic inflammatory response and endothelial dysfunction. Weel et al. 18 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 the induction of oxidative stress of placental explants acts as a DAMP and leads to the activation of NLRP3 19. We also demonstrated that after this initial placental activation of NLRP3, peripheral maternal innate immune cells also express NLPR3 activation, mainly between women with severe preeclampsia 20.

The clinical presentations of 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 may determine different degrees of NLRP3 inflammasome activation and these different responses may contribute to the different clinical scenarios observed in COVID-19. A similar process has been described in pregnancy, as controlled inflammation is essential for implantation of pregnancy, host defense and parturition. However, excessive inflammatory responses are correlated with several adverse pregnancy outcomes, especially preeclampsia 21.

The role of COVID-19 as a risk factor for preeclampsia is still controversial. The main reports indicate that preeclampsia is associated with severe cases of COVID-19, but it is not present in mild or moderate cases of the disease 22. It is important to consider that these patients with phenotypes of COVID-19 and preeclampsia share factors risk factors such as obesity, chronic high blood pressure, diabetes and other metabolic diseases. In view of the current analyses, it is only possible to speculate that COVID-19 and preeclampsia have common pathophysiological mechanisms, such as the activation of NLRP3, which act in synergism for a final clinical manifestation. Therefore, NLRP3 inhibitors can be a very effective treatment for PE. Meanwhile, interactions between NLRP3 inflammasome-regulated pathways may improve treatments for inflammation-related disorders such as PE and COVID-19.

DISCUSSION

The mechanisms underlying the association between COVID-19 and preeclampsia are unclear, but researchers have shown that SARS -CoV-2 can lead to dysfunction of the renin-angiotensin system and vasoconstriction by binding to angiotensin-converting enzyme 2 receptors. 21 The hallmark of preeclampsia is systematic endothelial dysfunction, which may share a common pathway with COVID-19 disease, as the vascular effects of SARS-CoV-2 infection are increasingly recognized. One study found that people with severe COVID-19 who were pregnant acquired preeclampsia-like clinical manifestations and were distinguishable by levels of biomarkers, including serum-soluble tyrosine kinase and placental growth factor. 22 Some studies have

shown that SARS-CoV-2 infection can create a pro-inflammatory state that is followed by systemic endothelial dysfunction and preeclampsia. 23, 24 Our finding is consistent with a 2020 study in Sweden that reported that pregnant women with COVID-19 had a higher prevalence of preeclampsia.[25]

Our review also interrogates whether SARS-CoV-2 infection was associated with preterm delivery, stillbirth, and lower birth weight, but not cesarean delivery, compared to the absence of SARS-CoV-2 infection. We also found that severe COVID-19 was strongly associated with preterm birth and other adverse perinatal outcomes. Some of these excessive risks may be related to preeclampsia, although SARS-CoV-2 infection can also cause exaggerated systemic inflammatory responses involved in the pathogenesis of preterm birth or in a suboptimal environment for fetal growth and development. Poor placental fetal vascular perfusion has been found in placental histopathological findings in COVID-19 patients at delivery, 26 which may contribute to fetal growth, stillbirth, and preterm delivery. A recent national quasi-experimental study in the Netherlands found that COVID-19 mitigation measures were associated with a reduced incidence of preterm birth. 27

The lack of knowledge about SARS-CoV-2 infection in pregnancy has raised urgent questions among obstetricians and neonatologists about the risk of maternal, fetal and neonatal morbidity and mortality. There is an urgent need for evidence to guide clinical decisions. Our findings suggest that SARS-CoV-2 infection increases the risk of preeclampsia, stillbirth, preterm birth, and NICU admission, and that severe COVID-19 illness in pregnancy is particularly problematic for maternal, fetal, and neonatal outcomes. adverse. Clinicians must be aware of these adverse outcomes when managing pregnancies in patients with COVID-19 and adopt effective strategies to prevent or reduce risks to patients and fetuses.

LIMITATIONS

We did not register our study in the International Prospective Register of Systematic Reviews (PROSPERO), and our literature search was restricted to publications in English. Although we have included a comprehensive number of results, we cannot rule out the possibility that some associations are spurious. Some of the included studies (14%) did not require a negative result for a PCR test to be included in the unexposed comparison group. 28, 29, 30, 31, 32, 33. The largest study that had data on confounders suggested that associations between COVID-19 and pregnancy outcomes were somewhat attenuated after adjustment, although risks remained high for most outcomes. 34 We were also unable to determine the clinical importance of some of the results. For example, we cannot confirm that all patients admitted to the NICU required intensive care. The reason for the preterm birth was unclear, including whether the preterm birth was medically indicated or spontaneous. As the data were observational, we cannot eliminate the possibility of residual confounding.

FINAL CONSIDERATIONS

There are currently several gaps about this virus and its effects, with limited data available on pregnant women infected with COVID-19. The main reports point out that preeclampsia is associated with severe cases of COVID-19, but is not present in mild or moderate cases of the disease. It is important to consider that these patients with COVID-19 and preeclampsia phenotypes share common risk factors such as obesity, chronic high blood pressure, diabetes, and other metabolic diseases. In view of the

current analyses, it is only possible to speculate that COVID-19 and preeclampsia have common pathophysiological mechanisms, such as the activation of NLRP3, which act in synergism for a final clinical manifestation. Therefore, NLRP3 inhibitors can be a very effective treatment for PE. Meanwhile, interactions between NLRP3 inflammasome-regulated pathways may improve treatments for inflammation-related disorders such as PE and COVID-19.

Pregnant women infected with COVID-19 must be closely monitored even after their etiologic tests turn negative, as they are still at great risk. Notably, this research has provided some strategies for the obstetric management of pregnant women with COVID-19. Collectively, these findings advocate expanded and urgent prenatal surveillance for pregnant women diagnosed with SARS-CoV-2 and comorbidities (preeclampsia). Aggressive mandatory intervention to effectively manage a severe respiratory infection must be the cornerstone of care for any pregnant woman with COVID-19. Future surveillance systems for COVID-19 cases need to include data on pregnancy status as well as maternal and fetal outcomes.

Future studies are needed to collect more robust data to further validate or substantiate these findings, better understand the pathophysiological pathways that explain these associations, and identify effective strategies to prevent adverse outcomes in pregnant women with COVID-19.

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