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LETTER TO THE EDITOR

Immunological environment shifts during pregnancy may affect the risk of developing severe complications in COVID-19 patients

1 | INTRODUCTION

The first case of coronavirus virus disease 2019 (COVID-19) was revealed in Wuhan in December 2019[1]; the virus spread in China and then globally.[2] According to the increasing growth rate of coronavirus cases, this outbreak was declared a Public Health Emergency of International Concern on January 30, 2020, by the WHO Emergency Committee.[3]

The most frequent symptoms in mild and moderate cases of COVID-19 were fever, anosmia, or shortness of breath, which appears to be more frequent in adults than children, as well as cough, dyspnea, and myalgia, among other clinical features.[4] The laboratory abnormalities included increased values of C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, and D-dimer.[4,5] According to the meta-analysis of AJ Rodriguez-Morales et al,[5] lymphopenia was detected in more than 40% of patients. The frequency of lymphopenia found suggests that COVID-19 acted on T lymphocytes, as does SARS-CoV, maybe including depletion of CD4 and CD8 cells.[5] Virus particles spread through the respiratory mucosa, initially using the ACE2 receptor at ciliated bronchial epithelial cells, and then infect other cells, which causes a "cytokine storm" in the body and generates a series of immune responses.[6] The "cytokine storm" with a hyper-innate inflammatory response in the lungs of COVID-19 patients is driven mostly by the IL-6, which is produced by monocytes and macrophages[7-9] and may serve as a predictive biomarker for disease severity[9] or a target for the therapy development.[8,10]

Because of the immune reaction severity, 20.3% of COVID-19 patients required intensive care unit, 32.8% presented with acute respiratory distress syndrome (ARDS), 6.2% with shock.[5] It has been shown that ARDS occurs even when the viral load decreases,[11,12] which suggests that the over-reactivity of the immune system and not the action of the virus are responsible for the occurrence of ARDS, and the attenuation of the "cytokine storm" by targeting several key steps in the process could bring about improved outcomes.[8,10,13]

In this regard, the urgent question that needs to be addressed promptly includes whether pregnant women with COVID-19 will develop distinct symptoms from non-pregnant and what are the reasons for that. This is of particular relevance to the fact that pregnant women infected with other respiratory viruses, for example, H1N1 influenza, Zika virus, and SARS-CoV were reported with more fetal adverse events.[14]

2 | DISCUSSION

The first part of the question has already been discussed in several studies,[15-19] while the underlying mechanisms are not clear yet. According to the systematic review of Yang et al,[15] clinical characteristics of pregnant women with COVID-19 did not differ from those of non-pregnant adults, while Qiancheng et al[18] have detected more leukocytosis and elevated C-reactive protein in pregnant than in non-pregnant women with COVID-19. No significant differences in gestational age, post-partum hemorrhage, and perineal resection rates between pregnant women with the clinical diagnosis of COVID-19 and pregnant women without COVID-19 were found.[16] Likewise, there were no significant differences in birth weight of neonates and neonatal asphyxia rates between the two groups.[16] Likewise, the SARS-CoV-2 infection during pregnancy was not associated with an increased risk of spontaneous abortion and spontaneous preterm birth.[17] Thereby, there is a clear tendency that COVID-19 disease progresses slowly in pregnant women and does not often result in fatal pregnancy complications.[17]

Consequently, the question arises whether the virus may affect the function of the placenta and increase the risk of miscarriage.[20] SARS-CoV-2 is known to use the SARS-CoV receptor ACE2 and the serine protease TMPRSS2 for entry and S protein priming,[21] while the placental microenvironment expresses both ACE2 receptor and TMPRSS2.[19,20,22,23] With that, the absence of any significant differences in ACE2 mRNA among the non-pregnant and normal pregnant subjects in the placental bed[24] can serve as the reason for the absence of any pregnancy-specific mechanisms of virus pathogenicity. While current literature does not support the intrauterine vertical transmission of SARS-CoV-2,[25-27] viral RNA in placental samples having not been found in the early study of Mulvey et al[19] was detected in subsequent ones.[28,29] With that, according to the histological examinations, the vascular complement deposition in the

placentas of COVID-19 patients was not abnormal, with only the signs of non-specific low-grade fetal vascular malperfusion characterized by focal avascular villi.[30,31]

A healthy human pregnancy requires the sustentation of active immunotolerance toward the semi-allogeneic fetus,[32,33] involving the suppression of effector functions and induction of tolerance, originally described as a Th2 skewing and now explained as a balance between Th1, Th2, Th17, Treg, and regulatory responses.[33-38] The protective benefits of the observed Th2 cell's rise in pregnancy[34] can be mediated by the up-regulation of Th2 response with the increase of IL-4 and IL-10, or down-regulation of a Th1 response,[35] or even via CD4+CD25+Treg cells.[36-38] Altogether, these mechanisms can prevent the excess systemic inflammatory reaction and the development of life-threatening complications as ARDS and MODS in COVID-19 patients. The presence of these beneficial effects precisely in SARS-CoV-2 infection may lie in the fact that the adaptive immune response of the COVID-19 patients is more likely to come before the peak of viral load, while the opposite is true for influenza patients.[26] This distinction in timing causes delayed depletion of vulnerable epithelial cells in the lungs in COVID-19 patients while enhancing the viral clearance in influenza patients.[14] According to the analysis, conducted by Du and Yuan,[39] delaying the onset or suppressing the adaptive immune response, or avoiding its interference with the innate immune response, might represent the potential treatment strategies for high-risk COVID-19 patients.

Thus, the foregoing not only explains the absence of severe outcomes in pregnant women with COVID-19 but also suggests a search for new drugs aimed at partial immunomodulation involving the suppression of effector functions and induction of tolerance, which will reduce the frequency of life-threatening complications, including ARDS.[13]

The existence of the temporary changes in the immune response during pregnancy represents themselves in the Th1 inflammation-like condition early in pregnancy, with the shift to a state of temporal Th2-skewed immune tolerance during the second trimester and a second shift during parturition[40,41] can be the limiting factor for the proposed hypothesis, and therefore, the effect of COVID-19 in pregnancy warrants further studies. With that, the idea that pregnant women are more susceptible to respiratory pathogens and thus may be more susceptible to SARS-CoV-2 than the general population[42] has not been confirmed yet, while the limited amount of data received so far, allows only hypothesis building and suggesting ideas for further research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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