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Editorial

COVID-19 in pregnancy

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Coronavirus Disease 2019 (COVID-19) is the most dramatic pandemic of the new millennium, and it has globally urged the scientific research without precedents. More recently, the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) has published the results of the INTERCOVID multinational cohort study, involving 43 institutions from 18 different countries (Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, United Kingdom, United States), in which 706 COVID-19 pregnant women and 1424 COVID-free pregnant women have been enrolled and studied from March to October 2020 [1]. COVID-19 women are resulted at higher risk for severe infections, intensive care unit admission, preeclampsia/eclampsia, maternal mortality, preterm birth, medically indicated preterm birth, severe neonatal morbidity index, and severe perinatal morbidity and mortality index [1]. Interestingly, COVID-19 women already at high risk for preeclampsia because of preexisting overweight, diabetes, hypertension, and cardiac or chronic respiratory diseases, have showed almost 4 times greater risk of developing preeclampsia/eclampsia [1]. Therefore, these findings should alert pregnant women and clinicians to implement strictly all the recommended COVID-19 preventive measures, such as respiratory hygiene by filtering facepiece 2 or 3 (FFP2 or FFP3) masks, physical distancing at least 1 meter, avoid interacting with sick people and spending time in crowded places, cleaning hands with sanitizer or soap and water. But what are the biomolecular reasons behind these results? There are essentially two orders of reasons, the former concerns with the immune system rearrangement of pregnant women, while the latter with the angiotensin-converting system of blood pressure control. As well known, during a healthy pregnancy there is an important shift from the cell-mediated immunity, the so-called T-helper 1 (T_h1) response, towards the humoral one, also termed T-helper 2 (T_h2) response, in order to protect the fetus by rejection, ensuring full maternal immune tolerance [2, 3]. In this way, the immune system of a pregnant woman is T_h1 depolarized and T_h2 polarized, a default defense less effective against intracellular or phagocytosable pathogens, such as viruses [4]. If we consider that the most serious COVID-19 occur precisely in those patients with a deficient T_h1 immune response, due to individual predisposition, pre-existing pathologies, or advanced age [4–6], a logical explanation about the higher risk for severe infections in pregnant women is obtained (Fig. 1). In addition, we know that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) enters the cells via angiotensin-converting enzyme 2 (ACE2) [7, 8], located in various tissues including the placenta, where it can exert its action and then pass into the fetus [9–11]. The placenta is a transient organ devoid of autonomic nerve terminals, and its main regulatory mechanism of perfusion is represented by the angiotensin-converting system [12]. Placental ACE2 exhibits a gestational age-dependent expression profile with higher levels in the first trimester, which so appears to be the most vulnerable gestational period for SARS-CoV-2 infection [13]. According to a secondary analysis of the World Association of Perinatal Medicine (WAPM) study, a multinational cohort study on 388 consecutive singleton pregnancies with laboratory-confirmed COVID-19 from February to April 2020 belonging to 73 centers spread across 22 different countries (Argentina, Australia, Belgium, Brazil, Colombia, Czech Republic, Finland, Germany, Greece, Israel, Italy, North Macedonia, Peru, Portugal, Republic of Kosovo, Romania, Russia, Serbia, Slovenia, Spain, Turkey, United States), early gestational age at infection, maternal ventilatory support, and low birthweight are the main determinants of adverse perinatal outcomes in fetuses with maternal COVID-19 [14]. Physiologically, ACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensin 2 (A2), a powerful vasoconstrictor, into angiotensin 1-7 (A1-7), a vasodilator peptide [7]. The extracellular domain of ACE2 is cleaved from the transmembrane domain by the enzyme *sheddase*, and its soluble form (sACE2) is released into the bloodstream and, ultimately, excreted in the urine [15]. The binding of SARS-CoV-2 spike protein and free-floating spike proteins with ubiquitous ACE2 receptors and sACE2 results in a down-regulation or loss of function [16], with subsequent onset of a blood pressure framework dominated by A2 prone to inflammation and hypertension (Fig. 1), which al-

lows to explain well the higher risk to develop preeclampsia/eclampsia in COVID-19 pregnant women. The occurrence of preeclampsia/eclampsia in general population is influenced by maternal race; likewise, the probability of developing a moderate or severe form of COVID-19 among pregnant women correlates with ethnicity, being higher in Hispanic than non-Hispanic females [17]. By virtue of all this new evidence, the International Society of Infectious Diseases in Obstetrics and Gynecology (ISIDOG) considers pregnancy as a risk factor for serious complications from SARS-CoV-2 infection, and pregnant women as a priority category in receiving COVID-19 vaccination [18]. Currently available data favor modRNA-based vaccines above vector-based vaccines during pregnancy and breastfeeding, although long-term pharmacovigilance is still lacking for both [19]; however, preliminary findings of modRNA vaccine safety in pregnant persons are encouraging to date [20].

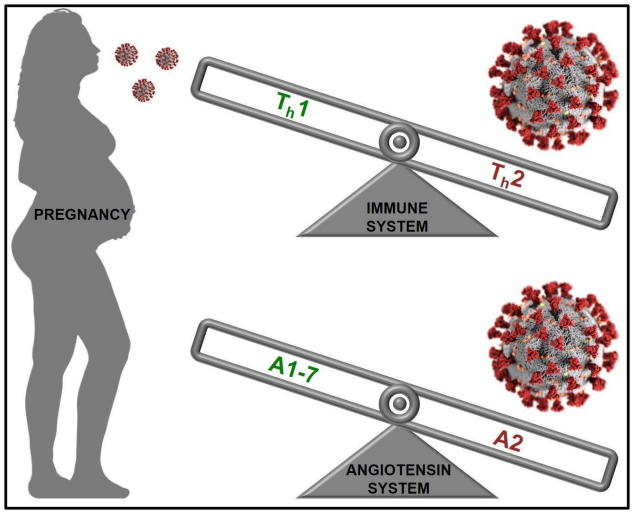

Fig. 1. The immune system during a healthy pregnancy is T_h2 polarized, a default defense that makes the pregnant woman more vulnerable to severe SARS-CoV-2 infection. Moreover, the interaction between the spike protein and ACE2/sACE2 creates an imbalance towards A2, which higher risk to develop preeclampsia/eclampsia [*the 3D illustration of SARS-CoV-2 has been drawn by Alissa Eckert, MS, and Dan Higgins, MAM, at the Centers for Disease Control and Prevention (CDC) of Atlanta, Georgia, USA, placed in the public domain and thus free of any copyright restrictions*].

Author contributions

LR conceived, designed and supervised the study, interpreted the data, prepared the figure with the related legend, and wrote the manuscript; GG analyzed the data; EA and GA performed the literature search. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest. LR is the Associate Editor of this journal; given his role as Associate Editor, he was not involved in the peer-review of this article and had no access to information regarding its peer-review.

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