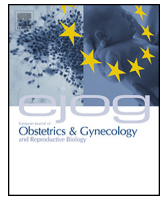




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Correspondence

COVID-19 during pregnancy: Potential risk for neurodevelopmental disorders in neonates?



Dear Editor

SARS-CoV-2 is a novel coronavirus associated with an acute pulmonary disease known as COVID-19. This emerging coronavirus is closely related genetically to the SARS-CoV-1 and uses the human angiotensin-converting enzyme 2 (hACE2) and transmembrane serine protease 2 (TMPRSS2) as host cell receptors. The binding between SARS-CoV-2 and these cell receptors leads to hyper-activation of the NF- κ B pathway and increased production of inflammatory cytokines including IL-6 and TNF α , which are implicated in the severe lung injury and poor clinical outcomes in patients with COVID-19 [1].

Although much attention has been placed on older adults populations for being a high-risk group susceptible to life-threatening respiratory and systemic conditions associated to SARS-CoV-2 infection, pregnant women should not be disregarded as high-risk population and should be considered in policies and public health strategies focusing on prevention and management of SARS-CoV-2 infection. Findings from a recent systematic review suggest lack of evidence for vertical transmission of SARS-CoV-2 [2], however studies evaluating the effects of inflammation dysregulation in pregnant women with SARS-CoV-2, the effects on the pathophysiology and genomic function of the placenta and the potential short- and long-term effects on children developmental outcomes are yet to be fully explored. On April 11, 2020, a study showed that pregnant women with SARS-CoV-2 infection had higher levels of IL-6 compared to non-pregnant women which may important implications in the development of fetuses [3].

There is growing evidence that prenatal infection and enhanced expression of cytokines are associated with an increased risk of autism spectrum disorder (ASD) and schizophrenia (SZ) in the offspring. Maternal immune activation appears to act as a “neurodevelopmental disease primer” increasing the susceptibility of individuals to the epigenetic alterations and environmental exposures that can interact in triggering disease-related symptoms later in life [4]. IL-6 has been treated as an indicator of maternal systemic inflammation with potential to influence placental-fetal interactions and subsequently fetal brain development and increased risk of offspring psychiatric disorders. Although the role of IL-6 in the pathogenesis of neurodevelopmental disorders is not fully understood, a longitudinal study showed alterations in

brain architecture, executive function, and working memory abilities in neonates at 2 years of age exposed to increased levels of IL-6 during pregnancy [5]. In addition, it has been found that maternal IL-6 is inversely associated with offspring cognition at 12-months age, which strengthen the assumption that maternal inflammation may constitute an intrauterine condition of particular importance in the context of potentially neuropsychiatric disorders [6].

Therefore, it is reasonable to hypothesize that cytokine storm and hyperinflammation found in pregnant women with SARS-CoV-2 infection may increase the risk for neurodevelopmental disorders in the neonates. Urgent research agenda should include assessment of inflammatory levels in pregnant women with COVID-19 and longitudinal evaluation of offspring neurodevelopmental outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
- [2] Martins-Filho PR, Santos VS, Santos Jr. H. To breastfeed or not to breastfeed? Lack of evidence on the presence of SARS-CoV-2 in breastmilk of pregnant women with COVID-19. *Rev Panam Salud Publica* 2020;44:e59.
- [3] Yin M, Zhang L, Deng G, Han C, Shen M, Sun H, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy in China: a retrospective cohort study. *MedRxiv* 2020, doi:<http://dx.doi.org/10.1101/2020.04.07.20053744>.
- [4] Estes ML, McAllister AK. Maternal immune activation: implications for neuropsychiatric disorders. *Science* 2016;353:772–7.
- [5] Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, et al. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. *Nat Neurosci* 2018;21:765–72.
- [6] Rasmussen JM, Graham AM, Entringer S, Gilmore JH, Styner M, Fair DA, et al. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. *Neuroimage* 2019;185:825–35.

Paulo Ricardo Martins-Filho*

Diego Moura Tanajura

Investigative Pathology Laboratory, Federal University of Sergipe,
Brazil

Hudson P. Santos Jr.
School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Victor Santana Santos
Centre for Epidemiology and Public Health, Federal University of Alagoas, Arapiraca, Brazil

* Corresponding author at: Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa, Rua Cláudio Batista, s/n. Sanatório, Aracaju, Sergipe, CEP: 49060-100 Brazil.

E-mail address: martins-filho@ufs.br (P. Martins-Filho).

Received 28 April 2020