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COVID-19 as a unique opportunity to unravel the link between prenatal maternal infection, brain development and neuropsychiatric disorders in offspring

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COVID-19 as a unique opportunity to unravel the link between prenatal maternal infection, brain development and neuropsychiatric disorders in offspring.

Study of the effects of prenatal maternal infection on early offspring brain development has long attracted the interest and endeavors of clinicians and neuroscientists.[1] Early reports on large-scale ecological data and further birth cohort studies analyzing biomarkers in pregnancy and early life of offspring have yielded evidence that in-utero exposure to infection increases neuropsychiatric disorder risk, particularly schizophrenia and autism spectrum disorders.[2, 3, 4] The main hypothesis derived from these studies is that activation of immune-inflammatory pathways during maternal infection may result in abnormal fetal brain development.[5] However, such a hypothesis requires detailed testing to reveal the pathogenic and pathophysiological mechanisms behind these neurodevelopmental alterations.

In the current historical milieu, two crucial circumstances converge that could help unravel this link between prenatal maternal infection and the risk of neuropsychiatric disturbances in the offspring. First, coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is by far the largest pandemic of our time.[6] Second, our capacity for thorough collection of epidemiological and clinical data, combined with accessibility to sophisticated biological research strategies in a scientific context of well-establish collaborative research networks, has enhanced understanding of the biological mechanisms underlying brain development.[7, 8]

The transmission dynamics of COVID-19 and the lack of an effective vaccine until at least the first half of 2021 suggest that the pandemic could affect up to one-third of the world's population.[9] Under this scenario, approximately 100 million pregnant women would be at potential risk of acquiring the SARS-CoV-2 infection, and therefore, there is growing concern about a dramatic increase of neurodevelopmental problems in the offspring of mothers infected during pregnancy in the coming years, similar to that observed after the 1918 influenza pandemic.[3, 9, 10] From a wider viewpoint, this concurrence could provide a unique opportunity for advancing and refining the hypothesis of how prenatal exposure to infection might jeopardize normal brain development, increasing the likelihood of later neuropsychiatric disorders.

Among the possible etiological and pathophysiological mechanisms by which COVID-19 maternal infection may interfere with fetal brain development, are the direct mechanisms, such as vertical mother-to-child transmission, and indirect, either as a result

of uteroplacental insufficiency from thrombosis or gestational hypoxia, or due to the prenatal effects of maternal immune/inflammatory response.[9, 11] Alteration of the maternal-fetal immune environment seems to be the key determinant behind breakdown in offspring brain development of women who have been infected during pregnancy[5]. Therefore, attention should especially focus on the effects of infection-induced maternal immune activation and the role of cytokines, chemokines, and other inflammatory markers.[5] In addition, whether infection alters brain development through specific infection-induced mechanisms or a common pathway, how susceptibility of genetic variations and epigenetic mechanisms interact with infection, differentially influence the risk of mental illness, or whether gestational timing is critical to increased vulnerability, are all still unresolved issues.[2, 12, 13] Finally, other possible factors that might affect brain development, such as high stress hormone levels (maternal cortisol and placental corticotrophin-releasing hormone), bacterial translocation from gut, and the role of maternal psychological stress (lockdowns, general worry about health, work conditions or salary restrictions, infotoxicity, etc.), must be quantified and corroborated.[2, 12]

All of the above leads to the conclusion that, as a high priority within the framework of the COVID-19 pandemic, design and implementation of translational research projects, integrating findings from epidemiological and pathophysiological studies, can elucidate the causal mechanisms by which brain development is affected by these prenatal insults. Now is the time to carry out population-based birth cohort studies of COVID-19–infected pregnant women from a diversity of racial, ethnic, and geographic groups which include long-term longitudinal follow-ups of their offspring, as well as comparisons with control populations of non-infected pregnant women.[12] Along this line, there have been several initiatives around the world, such as the United Kingdom Obstetric Surveillance System (UKOSS) study, which from March 1, 2020 to April 14, 2020, has already collected the perinatal outcomes of 427 pregnant women with confirmed SARS-CoV-2 infection from all 194 hospitals with obstetric units in the United Kingdom.[14] These studies provide the possibility to acquire biological (e.g., umbilical cord and placenta samples), clinical (e.g., maternal serum samples and neonatal filter paper blood samples) and neurocognitive (e.g., neurodevelopmental and neuropsychological scales) data that would enable the acquisition of invaluable genetic, metabolic, immunological and neurobehavioral information.[15] Such a large amount of information could overcome the limitations of previous studies and help unravel the complex relationship between maternal infection and later appearance of neurodevelopmental and neurobehavioral disturbances in the offspring. Such a challenging goal will require generous, long-term interdisciplinary collaboration by epidemiologists, geneticists, molecular/cellular neuroscientists, immunologists, microbiologists, gynecologists and obstetricians, neonatologists and

pediatricians, child and adolescent mental health professionals, and psychiatrists and psychologists.[9] An integrated, collaborative, interdisciplinary team which would have to work hard to overcome the logistical and financial barriers of design and implementation of long-term research projects, a clearly worthwhile effort outweighing the costs. This is why we are calling clinicians, researchers and the competent authorities in research investment and funding to action, so that from the tragedy of the COVID-19 crisis, we can seize the opportunity offered by a pandemic to advance in the knowledge of the etiopathogenesis of neurodevelopmental disorders.

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