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.

COVID-19 and the endometrium: inflammation as understanding

The onset of the coronavirus disease 2019 (COVID-19) pandemic was marked by fear—fear of illness and death as well as fear of the unknown. For those of us in the field of reproductive medicine, this fear of the unknown translated directly into the clinical care of our patients, especially for those with little information available for counseling regarding the safety of conception or potential implications for their hard-won pregnancies. For the larger population, we saw this fear play out in vaccine hesitancy and refusal as well as in the conflicting advice that we as a field gave to our patients regarding the best way to approach COVID-19 with reproductive age women trying to conceive. Now, nearly 3 years later, we have begun to replace this fear with knowledge, and we are on our way to develop knowledge into understanding.

First, the knowledge: we now have a significant body of literature supporting the impact of COVID-19 on pregnancy outcomes. Significantly, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during pregnancy is associated with increased rates of preeclampsia, preterm birth, and stillbirth, with higher incidence of adverse outcomes in patients with severe disease compared with mild disease (1). This is despite the fact that the SARS-CoV-2 virus itself does not appear to readily cross the placenta, possibly owing to the low placental expression of angiotensin-converting enzyme 2 and transmembrane serine protease 2. Moreover, the maternal to fetal transmission of COVID 19 is rare (1, 2).

We also have a significant body of literature reassuring us regarding the safety of COVID-19 vaccination in pregnancy or in those trying to conceive. In contrast to SARS-CoV-2 infection itself, the COVID-19 vaccination does not increase the risk of perinatal morbidity, including preterm delivery, small for gestational age, or neonatal intensive care admissions (3). Studies have similarly shown no increased risk of spontaneous abortion after receiving the COVID-19 vaccination during pregnancy (3).

Finally, we have also accumulated knowledge on the impact of COVID-19 infection and vaccination on menstrual function. First reported by women and then confirmed by observational studies, SARS-CoV-2 vaccination, and to a lesser extent potentially the infection itself, does impact women's menstrual cycles. Data from the Nurses Health Study have documented menstrual cycle disturbances lasting up to 6 months after COVID vaccination (4).

Now, the understanding. How does COVID-19 infection impact perinatal outcomes if the virus does not cross the placenta? By what mechanism does COVID-19 (or the vaccine) potentially impact menstrual function? Much of our knowledge until now has been speculative. We have understood that COVID-19, as an illness, imparts much of its morbidity not from the infection itself but rather from the immune response to the virus. Viewing COVID-19 as an inflammatory process has helped to create hypotheses for the differential in disease severity between those affected in pregnancy and other populations as well as between those with risk factors such as hypertension and obesity; it has also given rise to the hypotheses regarding the development of long-COVID and other post-COVID associated morbidities.

How does this view of COVID-19 as an inflammatory state translate into our understanding of COVID-19's impact on pregnancy outcomes and menstrual function? In this month's issue of *Fertility and Sterility*, de Miguel-Gómez and colleagues describe their findings on the basis of ribonucleic acid (RNA) sequencing analyses of the endometrial biopsies taken from women with and without COVID-19 infections (5). Despite previous data that failed to show a mechanism for direct SARS-CoV-2 infection of the endometrium, their study presents evidence of altered gene expression in the endometrium of women infected with SARS-CoV-2. In the study, endometrial biopsy samples were taken from 14 women hospitalized with mild to severe COVID-19 infection and 10 women undergoing hysteroscopy for benign indications without known COVID-19 diagnosis who served as controls; 18 of these were ultimately analyzed for gene expression using RNA sequencing. Endometrial biopsies from the patients with COVID-19 demonstrated differential gene expression compared with controls; up-regulated pathways included those corresponding to viral response, interferon-1 production, and the formation of neutrophil extracellular traps (or NET) among others, whereas down-regulated pathways also included immune regulation pathways, including T-cell activation and cytokine regulation pathways. Although the study was small, as a pilot, the data suggest that COVID-19 impacts the endometrium via inflammatory pathway as part of the larger systemic inflammatory response to the virus.

As the investigators point out, the endometrium is not "immune" to inflammatory challenges and systemic inflammatory responses that are known to underlie autoimmune diseases such as systemic lupus erythematosus. These may also be the etiologic agents of adverse perinatal outcomes (such as high rates of preeclampsia) observed in pregnant patients with obesity, endometriosis, and other chronic conditions. The candidate genes and pathways identified in this study should serve as a starting point for future research not just for COVID-19 but for the mechanism underlying the role of inflammatory insult in adverse pregnancy outcomes.

However, caution should be observed in interpreting a pilot study as more than a pilot study. The sample size was small, and ultimately only 18 endometrial biopsies were analyzed. Of the 9 samples each from the control and COVID-19 groups, 2 (1 from each group) were removed as outliers. Additionally, 2 of the samples from the COVID group clustered with the control group and were not analyzed in the final analysis; the investigators concluded that one of these patients may have had a false positive COVID-19 diagnosis. Therefore, it is wise to be cautious about drawing too many conclusions from a dataset of 6 patients with COVID-19. The sample was also heterogenous, although the investigators do state that they were

able to control for the phase of the menstrual cycle in their analysis. Given that the controls did not have any viral illness, it is also impossible to distinguish whether the gene expression alterations observed are unique to COVID-19 or true of all system viral infection.

Moreover, SARS-CoV-2 is, for a good reason, becoming one of the most well-studied viruses of our day. As we replace fear with knowledge, we can view our accumulated data as a challenge to better characterize the mechanisms underpinning normal and abnormal pregnancy establishment as well as outcomes. As this study suggests, the inflammatory response from COVID-19 (not the virus itself) impacts the endometrium by up-regulating and down-regulating key pathways involved in immune response. The implication is that these dysregulated pathways will then affect menstrual function and implantation, leading to placenta-mediated morbidities such as preeclampsia and stillbirth. It is now our task to further explore this relationship to help our field achieve a true understanding.

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