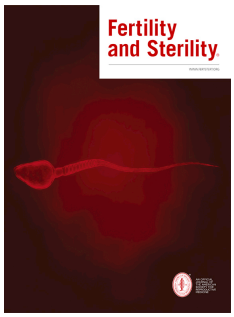
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



COVID-19 and the Endometrium: Inflammation as Understanding

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Invited Commentary

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The onset of the COVID-19 pandemic was marked by fear. Fear of illness and death. But also fear of the unknown. For those of us in reproductive medicine, this fear of the unknown translated directly into the clinical care of our patients, for whom little information was available to counseling regarding 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, and in the conflicting advice we as a field gave to our patients regarding the best way to approach COVID-19 as reproductive age women trying to conceive. Now, nearly three years later, we have begun to replace fear with knowledge, and we are on our way to developing knowledge into understanding.

First, the knowledge: we now have a significant body of literature supporting the impact of COVID-19 on pregnancy outcomes. Significantly, SARS-CoV-2 infection during pregnancy is associated with higher rates of preeclampsia, preterm birth, and stillbirth, with higher incidence of adverse outcomes in patients with severe compared to mild disease(1). This is despite the fact that the SARS-CoV-2 virus itself does not appear to readily cross the placenta, possibly due to low placental expression of angiotensin-converting enzyme 2 and transmembrane serine protease 2, and 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, vaccination for COVID-19 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 for spontaneous abortion following COVID-19 vaccination in pregnancy(3).

Finally, we have also accumulated knowledge of 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 infection, does impact women's menstrual cycles. Data from the Nurses Health Study have documented menstrual cycle disturbances 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 severity risk between those affected in pregnancy and other populations and between those with risk factors such as hypertension and obesity; it has also given rise to 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'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 based on RNA sequencing analyses of endometrial biopsies taken from women with and without COVID-19 infections[5]. Their study presents evidence that gene expression is altered in the endometrium of women infected with SARS-CoV-2, despite prior data from their group and others that failed to show a mechanism for direct SARS-CoV-2 infection of the endometrium. 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 COVID-19 patients demonstrated differential gene expression compared to controls; upregulated pathways included those corresponding to viral response, interferon-1 (IFN-1) production, and the formation of neutrophil extracellular traps (or NET) among others, while downregulated 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 authors point out, the endometrium is not "immune" to inflammatory challenges, and systemic inflammatory responses, while known to underlie auto-immune diseases such as systemic lupus erythematosus, may also be the etiologic agents of adverse perinatal outcomes (such as higher 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.

Caution should be observed, however, 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) was removed as an outlier. Additionally, 2 of the samples from the COVID group clustered with the control group and were not analyzed in the final analysis; the authors concluded that one of these patients may have had a false positive COVID-19 diagnosis. It is therefore wise to be cautious about drawing too many conclusions from a dataset of 6 COVID-19 patients. The sample was also heterogenous, although the authors 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 if the gene expression alterations observed are unique to COVID-19 or true of all system viral infection.

SARS-CoV-2 is, for 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 and outcomes. As this study suggests, the inflammatory response from COVID-19 (not the virus itself) impacts the endometrium by upregulating and downregulating 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 pre-eclampsia and stillbirth. It is now our task to further explore this relationship to help our field achieve a true understanding.

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