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.

Endometrial susceptibility to SARS CoV-2: explained by gene expression across the menstrual cycle?

On March 11, 2020, the World Health Organization declared the outbreak of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) a global pandemic, reporting community-scale transmission worldwide with more than 8 million cases of confirmed coronavirus disease (COVID-19). On March 17, the American Society for Reproductive Medicine provided early key recommendations, updated and affirmed on March 30, including suspending initiation of new treatment cycles aimed at achieving pregnancy. The European Society of Human Reproduction and Embryology provided similar recommendations that expanded even further to include consideration of avoidance of spontaneous conception. These recommendations were made in the infancy of the pandemic when little was known about the implications of the novel coronavirus on implantation and pregnancy. Over the past several months, new developments in molecular virology and immunobiology of SARS-CoV-2 have improved our understanding of the novel coronavirus. In light of the rapidly expanding knowledge base and the realization that care cannot be paused indefinitely, fertility clinics around the world are beginning to resume treatment.

As fertility care recommences, the potential impact of SARS-CoV-2 on implantation and early pregnancy is increasingly relevant. Understanding the pathophysiology of the virus and the target tissues at a molecular level can help clarify the potential short- and long-term implications of infection on implantation, miscarriage, the intrauterine milieu, the placenta, and pregnancy and neonatal outcomes (1).

The genome sequence of SARS-CoV-2 is similar to, but distinct from the two other coronaviruses, as it has about 80% sequence identity with SARS-CoV and about 50% with MERS-Cov-2. Similar to SARS-CoV, the spike (S) protein of SARS-CoV-2 facilitates viral entry into target cells. Entry depends on binding of the S1 subunit of the S protein to a cellular receptor. Multiple studies have also confirmed that SARS-CoV-2 engages angiotensin-converting enzyme 2 (*ACE2*) as the entry receptor. In addition, viral entry depends on priming cleavage of the S protein, between S1 and S2, and activating cleavage on the S2′ site. Depending on virus strains and cell types, proteins may be cleaved by one or several host proteases, including furin, trypsin, cathepsins, transmembrane protease serine protease-2 (*TMPRSS2*), or *TMPRSS4* (2–4).

To date, the impact of SARS-CoV-2 on endometrial lining and implantation remains largely unknown, so the study by Henarejos-Castillo et al. (5) is of utmost importance. The authors assessed endometrial susceptibility to SARS-CoV-2 infection by measuring endometrial *ACE2*, *TMPRSS2*, *TMPRSS4*, cathepsin B and L (*CTSB* and *CTSL*, respectively), *FURIN*, MX dynamin-like GTPase 1 (*MX1*), and Basigin (*BSG*) gene expression. The group used public transcriptomic data sets to evaluate the risk of endometrial SARS-CoV-2 infection. Gene expression data from five studies including 112 women with normal endometrial pathology was used to characterize receptor expression throughout the menstrual cycle. The study population included 29 samples in the proliferative phase, 29 samples in early secretory phase, 43 in the medium secretory phase, and eight in the late secretory phase. A relative expression value of low, medium, and high expression was established. The thresholds correspond to 1% to 10%, 11% to 50%, and 51% to 100% categories of gene expression values of the entire integrated data set.

The authors reported high expression of *TMPRSS4*, *CTSB*, *CTSL*, *FURIN*, *MX1*, and *BSG* throughout the menstrual cycle (5). Notably, *ACE2* expression was found to be low, and *TMPRSS2* was moderately expressed throughout the menstrual cycle. Expression of viral proteins showed statistically significant changes at different stages of the cycle, except for *TMPRSS2* which remained relatively constant. Overall, all genes showed increased expression during the early secretory to midsecretory phase. The authors also reported a positive correlation in *ACE2* and *TMPRSS4* expression during the early secretory phase as well as a weak but positive correlation in *ACE2*, *TMPRSS4*, and *CTSL* expression during the window of implantation. The group also found a positive correlation between age and expression of most viral genes including *ACE2*, *TMPRSS4*, *CTSL*, and *CTSB* at different stages of the menstrual cycle, suggesting that older women may be at increased risk of SARS-CoV-2 endometrial infection.

Overall, the findings of this study (5) are reassuring and suggest low risk of endometrial infection by SARS-CoV-2. However, low expression of *ACE2*, the major cell surface receptor used by SARS-CoV-2, does not exclude the risk of endometrial infection because other proteases such as *TMPRSS4*, *CTSL*, *CTSB*, and *FURIN* show high expression during certain periods of the menstrual cycle. However, it is important to note that none of the highly expressed proteases reported in this study are known to initiate SARS-CoV-2 infection.

The authors accurately point to several limitations in the study. Because the data are extracted from existing data sets, the inclusion criteria for the selected studies may not represent the population contemplating conception or fertility treatment, and the reliability of the reported results depends on the quality of the initial studies. In addition, the genetic profile of individuals may vary depending on age, ethnicity, medication use, and underlying medical conditions such as endometriosis. The results of this study may not be generalizable to patients considering conception. As the authors suggest, the endometrial genetic profile changes throughout the menstrual cycle; the true risk of infection may primarily depend on protein expression during the window of implantation. Additionally, the suggestion that *ACE2* expression increases with age is not quantified clinically. What is the degree of increase? Does this increase reflect a clinical risk? The small sample size used for the age-related analysis should also be taken into account.

In conclusion, existing evidence suggests that expression of SARS-CoV-2 infection-related genes varies with age and

menstrual cycle phase, with *ACE2* expression increasing with female age. Overall, the endometrium appears to have low susceptibility to SARS-CoV-2 infection due to low *ACE2* and *TMPRSS2* expression; this susceptibility could vary depending on viral cell entry mechanisms. Further study of endometrial tissue from women of reproductive age infected with COVID-19 will help determine whether the retrospective molecular characterization of the endometrium translates to clinically accurate predictions.

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