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.

Triggered with COVID: What are my chances, Doc?

On March 17, 2020, the fertility world was disrupted when the American Society for Reproductive Medicine recommended halting treatment cycles as coronavirus disease 2019 (COVID-19) was recognized as a global pandemic. We have come a long way since that pivotal time, and thankfully, infertility treatment has resumed, notwithstanding large alterations in the patient care setting. These changes have included pervasive telehealth use; strains upon personnel, medical equipment, and supply chains; and patient fears of cycle cancellation should they become acutely infected. Despite mobilization of vaccines to protect against COVID-19, vaccine hesitancy and delayed global access to vaccination have helped fuel the emergence of mutant strains that continue to stress our healthcare systems broadly and fertility care specifically. From the beginning of the pandemic, the spread of COVID-19 raised questions about how infection with COVID-19 impacts fertility and pregnancy outcomes. Thankfully, there are increasing data reassuring us that neither COVID-19 infection nor its vaccines have long-term fertility effects. Even so, the impact of acute COVID-19 infection on cycle outcomes and early fetal development remains a potential reason for cycle cancellation, and the outcomes of in vitro fertilization (IVF) and embryo transfer in the setting of active COVID-19 infection are largely unknown.

As we round out the second year of the pandemic, we are presented with a timely study by Boudry et al. (1) in this month's issue of *Fertility and Sterility*. Boudry et al. (1) recruited female IVF patients after routine preprocedural screening who were found to be acutely infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibiting mild or no symptoms within 48 hours of retrieval. Given the uncertainty of acute SARS-CoV-2 infection on cycle outcomes as well as the risk of progression to more severe illness, the investigators performed a freeze-only cycle on any patients who had confirmed SARS-CoV-2 infection and desired to continue to retrieval. This allowed the investigators to collect follicle and endometrial specimens. The investigators analyzed samples from a total of 16 patients, and the primary findings showed a lack of any SARS-CoV-2 viral ribonucleic acid in follicular fluid, cumulus cells, or endometrial tissue at the time of retrieval (1).

While it is biologically plausible that SARS-CoV-2 may infect reproductive tissues, because of the expression of ACE2 and TMPRSS2 proteins on reproductive tissues (shown to function as a viral docking cell entry receptor and spike protein "priming" factor, respectively (2)), the study by Boudry et al. (1) is in line with prior work that has also not detected virus in tissues in the reproductive tract. The investigators cite Kteily et al. (3) who performed a similar study in Belgium during the same time frame. Kteily et al. (3) did not identify viral ribonucleic acid in vaginal fluid, ovarian tissue, follicular fluid, or semen samples from 20 patients who had tested positive for SARS-CoV-2 on nasopharyngeal swabs. Another study conducted by Takmaz et al.(4) in Turkey also did not identify SARS-CoV-2 on vaginal swabs in 38 women with COVID-19 pneumonia.

The study by Boudry et al. (1) also attempted to determine the effect of COVID-19 at the time of retrieval on IVF outcomes. The investigators report that embryologic outcomes were comparable between infected and uninfected patients in their clinic, but data are not included in the study. They also evaluated outcomes for patients included in this study who had previously had an IVF cycle as well as data for those who later underwent a subsequent cycle. Here Boudry et al. (1) again report that acute COVID-19 infection did not significantly alter fertilization and embryo development. It should be noted, however, that of the acutely infected patients, 25% ($n = 4$) had no embryos to freeze, and 3 of those 4 had successfully generated embryos in previous cycles. Three of 4 women from this same group cycled again after recovery from COVID-19, and all 3 women produced embryos for transfer and/or freeze. This raises the question from the audience of whether COVID-19 infection may have been detrimental for these patients in terms of the likelihood of producing embryos, but the small sample size precludes drawing any definitive conclusions. Finally, the investigators present findings from patients who returned for frozen embryo transfer (again, after recovery from COVID-19 infection), and they found that live birth was possible using embryos from patients who were acutely infected with COVID-19 at retrieval. In another recent study, Orvieto et al. (5) reported a decrease in the proportion of top-quality embryos for IVF cycles conducted within 90 days after COVID-19 infection for either the male or female partner, when compared with cycles performed before infection for the same couples; the impact of COVID-19 on embryo development remains an open question.

There are several limitations of the study that are worthy of consideration. First, as mentioned, despite the inclusion of all eligible patients over the course of 9 months, the sample size remained small. Next, the patients included in the study sample had primarily asymptomatic COVID-19 cases, with only 6 of the 16 patients exhibiting any symptoms. Patients with moderate or severe symptoms, and possibly a higher viral load, were excluded, and thus, whether the SARS-CoV-2 virus would still be absent in these tissues in the setting of a more severe infection remains unknown. Last, the rate of positive SARS-CoV-2 tests in the overall patient population was a low 0.53% in this study. The positivity rate is notably lower than the 6% rate reported by Kteily et al. (3), whose study was performed in the same city and time frame, although this difference may be explained by careful screening before initiating the IVF cycle.

Ultimately, the study conducted by Boudry et al. (1) is a valuable contribution to fertility research in these unprecedented times. The investigators found that for patients with mild or asymptomatic infections, SARS-CoV-2 does not appear to disseminate in the follicles or endometrium, and critically, these patients can still create embryos that lead to live birth. As additional studies assess reproductive parameters during

and after COVID-19 infection, the impact of COVID-19 on IVF and embryo transfer outcomes will become clearer.

Although a small study, the novel and timely findings presented by Boudry et al. (1) provide evidence that, after shared decision-making and discussion with the treatment team, it is reasonable to proceed with retrieval for patients with a newly diagnosed mild or asymptomatic COVID-19 infection. For patients with active COVID-19 infection before retrieval, continuing a policy of freeze-all cycles seems prudent until there are more data available regarding the safety and impact of COVID-19 on embryo transfer and early pregnancy outcomes.

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