Over the past 2.5 years, the global COVID-19 pandemic has killed millions of people worldwide, with consequences for every sector of the global economy, most notably, the health care system. Every medical specialty has been affected by the pandemic, including reproductive health care and assisted reproductive technology (ART). In the early, prevaccination days of the pandemic, resource scarcity and lack of knowledge about the implications of SARS-CoV-2 infection for fertility and pregnancy led to clinical guidelines that advised the temporary cessation of ART and diversion of resources toward helping the frontline fight against COVID-19. Today, thanks in large part to the advent of vaccines against SARS-CoV-2, the fatality and severity of COVID-19 have decreased substantially.

With the advent of these vaccines, questions arose regarding their implications for reproductive health, resulting in substantial vaccine hesitancy in some populations. Reassuringly, current studies have found that COVID-19 messenger RNA vaccines are not associated with adverse fertility, ART, or early pregnancy outcomes.1-3 In their study, Shi et al4 reported on the association of inactivated COVID-19 vaccination with ongoing pregnancy rates after in vitro fertilization (IVF) with a fresh embryo transfer. The authors found that, in China, patients in an ART center who were vaccinated 30 days or less or between 30 and 60 days before undergoing IVF had lower rates of ongoing pregnancy (34.3% and 36.2%, respectively) than patients who underwent IVF 91 days or more after COVID-19 vaccination (56.3%). After adjusting for confounders, Shi et al4 observed that the adjusted risk ratio (aRR) for ongoing pregnancy was lower in those who were vaccinated 30 days or less (aRR, 0.61; 95% CI, 0.33-0.91) or 30 to 60 days (aRR, 0.63; 95% CI, 0.42-0.85) before undergoing IVF compared with unvaccinated participants, whereas there was no difference between those who had been vaccinated more than 60 days before IVF and those who were unvaccinated. Shi et al4 concluded that patients undergoing IVF with a fresh embryo transfer may need to delay treatment for at least 60 days after being vaccinated.

Of importance, the vaccines received by participants in the study by Shi et al4 were all inactivated-virus vaccines that were available in China where the study was performed. These results should, therefore, be generalized with extreme caution, as they may not be applicable or reproducible in the US, where most of the vaccines administered have been mRNA based (eg, BNT162b2 [Pfizer-BioNTech] and mRNA-1273 [Moderna]).5 Studies of mRNA vaccines have not shown that they have adverse ART outcomes. It is critical to delineate the mechanisms by which the inactivated-virus vaccines (perhaps uniquely among COVID-19 vaccines) could affect pregnancy rates.

In contrast to other studies, the study by Shi et al4 included participants in the vaccinated group who received their second vaccine dose while in the middle of ART treatment. Although the authors noted that most patients did not experience adverse effects after the second dose of the vaccine, it is possible that the acute immune reaction could affect early pregnancy implantation and development. Beyond vaccine type and vaccination timing, the study findings may not be generalizable worldwide given the low rates of SARS-CoV-2 infection in China during the study period. Shi et al4 had to exclude only 33 participants of the nearly 8000 patients who were screened for the study. In contrast, it is estimated that more than 80% of the US population has been infected at least once with SARS-CoV-2.6 Public health policies in response to infectious disease pandemics vary widely between the US and China; thus, conclusions from this single study should be taken with caution and put in the appropriate context.
Shi et al addressed an important question with a large group of patients, but there are a couple of important limitations to discuss. Although the overall sample size of the study is large, the subgroups who received vaccination 30 days or less (n = 35) and 30 to 60 days (n = 58) before undergoing IVF were relatively small. In addition, patients in the 2 subgroups were considerably older than those who had been vaccinated for a longer interval of time before undergoing IVF. Although age was included as a potential confounder in the adjusted analysis, it is possible that residual confounding remains, especially given the nonrandomized nature of the study.

If these data are substantiated, they may alter the counseling given to patients who are planning fertility, specifically regarding inactivated vaccine use. Extrapolating these findings broadly could be a public health concern if the recommendation to delay ART treatment after COVID-19 vaccination disincentivizes vaccine uptake. There are a plethora of data that detail adverse outcomes in unvaccinated pregnant people with COVID-19.\(^\text{7}\) As the number of COVID-19 variants increases and vaccine-induced immunity wanes with time, recommendations for booster shots may compound this problem if patients feel that their reproductive priorities are at odds with public health recommendations.

It is now well accepted that COVID-19 is not going away. Further studies are needed to help us better understand the potential short- and long-term consequences of vaccination status by vaccine type, ART outcomes, and the way in which policies or recommendations that limit or discourage access to reproductive health care affect patients' well-being.

ARTICLE INFORMATION
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