



Commentary

Data-Driven Commentary on SARS-CoV-2 Infection, Vaccination, and Fertility

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A recent study by Wesselink et al. (*Am J Epidemiol.* 2022;191(XX):XXXX–XXXX) adds to the growing body of research finding that vaccination for coronavirus disease 2019 (COVID-19) is safe for individuals either seeking pregnancy or who are pregnant. The study's authors found no effect of COVID-19 vaccination on fecundity in a population of individuals with no known infertility who were attempting conception. The finding reinforces the messaging of the American Society for Reproductive Medicine COVID-19 Task Force, the aim of which is to provide data-driven recommendations to individuals contemplating pregnancy in the face of the COVID-19 pandemic. As safe and effective COVID-19 vaccines became available, and with an increasing number of studies showing a heightened risk of severe disease during pregnancy, an important role of the Task Force is to encourage vaccination during the preconceptional window and in early pregnancy. The Task Force supports ongoing research to address gaps in knowledge about safe and effective therapies and preventive measures for individuals contemplating pregnancy and during pregnancy. Such research will help optimize care for reproductive-age individuals in the face of current and future health crises.

COVID-19; fertility; pandemic; pregnancy; vaccination; vaccine hesitancy

Abbreviations: ASRM, American Society for Reproductive Medicine; COVID-19, coronavirus disease 2019; PRESTO, Pregnancy Study Online; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Reassuring data continue to emerge about the safety of vaccination on reproductive health outcomes and the adverse effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on fertility and pregnancy outcomes (1). The development of safe and effective vaccines against coronavirus disease 2019 (COVID-19) in 2020 ushered in an era of hope in the global COVID-19 pandemic response. Unfortunately, because of study-design decisions that excluded pregnant persons from phase 3 clinical vaccine trials, few published data to date specifically relate to assessment of the exposure to COVID-19 vaccination on fertility and early pregnancy outcomes (2). This lack of high-quality information regarding vaccine safety and efficacy in pregnant persons, in those seeking pregnancy, and in

reproductive-age people contributed to low vaccine uptake in these groups due to concerns about potential risks (3, 4). At the same time, serious adverse maternal, fetal, and neonatal outcomes of COVID-19 infection in pregnancy have been increasingly recognized and well documented (5–7). These outcomes heightened the need for broad access to and acceptance of vaccination as the most effective prevention tool available. The American Society for Reproductive Medicine (ASRM) COVID-19 Task Force has spoken with a strong voice to encourage vaccination of individuals contemplating pregnancy and during pregnancy as a means of providing protection from the untoward effects of COVID-19 in these discrete groups (8).

Based on concerns about theoretical risks, and despite an increasing awareness of higher rates of morbidity and mortality with COVID-19 infection during pregnancy, pregnant patients and those seeking pregnancy have been forced to rely on low-quality data in case reports, postmarketing information, and extrapolation of high-quality data from

randomized studies that enrolled predominantly older adults. The intentional exclusion of pregnant persons and those intending to become pregnant from most types of vaccine research stems from interpretation of federal research regulations outlined in part 46 of the Common Rule (45 Code of Federal Regulations 46) (9). Subpart B focuses on additional protections for pregnant women, fetuses, and neonates and requires preclinical studies prior to human studies and an assessment that interventions “hold out the prospect of direct benefit for the women or the fetus” or “the risk to the fetus is not greater than minimal” (9). In the absence of clear and consistent communication as vaccine safety was studied, and despite the lack of a plausible biological mechanism, conspiracy theories about vaccination spread rapidly through global social media communication networks. This harmful propaganda has created doubt for many people about the intentions and capabilities of public health efforts, the medical system, pharmaceutical companies, and the process of vaccine manufacturing. Global hesitancy about COVID-19 vaccination in pregnant persons and those seeking pregnancy has emerged as a major barrier to public health efforts (10–12).

As an example, early disinformation about vaccination cited the development of antibodies against syncytin-1, a cell–cell fusion protein that is essential for placental formation. Although these and other myths were rapidly debunked, they left an indelible mark on vaccination campaigns (13–15). Another wave of negative messaging on social media focused on the impact of COVID-19 vaccination on menstruation. Fortunately, emerging data are reassuring. In an initial study of 4,000 menstruating women who did or did not receive vaccination, researchers found a weak association with change of less than 1 day in cycle interval and no association between vaccination and length of menses (16). Unfortunately, it can be difficult to change or rescind an established false narrative, even as high-quality data become available.

Key subgroups with increased vaccine hesitancy include individuals who are pregnant or who are trying to conceive, who cite concerns about potential negative effects on fertility and offspring (17). Although the body of literature is growing, few studies have focused on vaccination and infection exposure during the critical periconception period and the first several weeks of pregnancy. Studies of men have shown that sperm parameters are similar, irrespective of vaccination status (18). Vaccination prior to and during pregnancy has emerged as an important strategy aimed at reducing morbidity and mortality. In addition, COVID-19 vaccination during pregnancy generates spike protein antibodies in the infant that persist through 6 months of age (19). There is growing consensus in the scientific community about the need for a paradigm shift in the design of clinical trials to generate high-quality evidence that is specific to people who are pregnant and those of reproductive age (20–24). In an attempt to avoid a prolonged delay between the identification of a new risk and documentation of outcomes, the safe inclusion of all groups who stand to benefit from the data should be considered at the study-design phase.

We read the recent study by Wesselink et al. (25) with great interest because it provides reassuring data regarding

vaccine safety for those contemplating pregnancy. The researchers investigated the important, yet understudied, question of whether any associations exist among COVID-19 vaccination, SARS-CoV-2 infection, and fecundity. The investigation included couples in the Pregnancy Study Online (PRESTO) preconception cohort study who enrolled in the 11 months onward from first vaccine availability. Data were collected from December 2020 through November 2021, and the analysis was restricted to those trying to conceive for 6 months or less without use of fertility treatment at the time of enrollment. The final sample included 2,126 couples. A total of 1,369 male partners were included by invitation from the female participant, and male information was collected both from the male partner directly and by female report. As for all PRESTO enrollees, medical history and sociodemographic information had been collected at baseline. Additional surveys were sent every 8 weeks for up to 12 months, and questionnaires continued during pregnancy and the postpartum period. In response to vaccine availability in December 2020, the baseline and early pregnancy questionnaires were changed to reflect COVID-19 vaccination status, type of vaccine, and date(s) of administration. Self-reported information was gathered regarding COVID-19 infection and, if applicable, the date of a positive SARS-CoV-2 test. Menstrual cycle and early pregnancy data were collected and included typical cycle length and, where applicable, estimated date of conception, pregnancy confirmation, and information on pregnancy loss.

Wesselink et al. (25) conducted their analysis with a single observation per menstrual cycle, stratifying participants at each time point as having received none, 1, or 2 vaccine doses. For analysis of SARS-CoV-2 infection, participants were also evaluated with a single observation per menstrual cycle and were considered to have had infection if they tested positive by the first day of that cycle. A fecundability ratio was calculated, as was the per-cycle probability of conception comparing exposed and unexposed individuals. Couples were followed until pregnancy or the occurrence of a censoring event (i.e., initiation of fertility treatment, cessation of pregnancy attempt, loss to follow-up, or 12 cycles of pregnancy attempt), whichever came first. Multivariable regression was performed evaluating potential confounding factors (e.g., age, smoking status, body mass index, race, menstrual cycle regularity).

Most of the population (85%) identified as non-Hispanic White with high educational attainment, high household income, and private health insurance. Vaccination rates for both male and female partners were high (74% and 73%, respectively). The analyses revealed several key findings: 1) Vaccination (either 1 or 2 doses) was not associated with improved or reduced fecundability in either partner; 2) infection with SARS-CoV-2 was not associated with reduced fecundability in women and was only transiently associated with reduced fecundability in men; and 3) there were no observed differences among vaccine brands. It should be noted that for men in the acute phase after SARS-CoV-2 infection (i.e., within 30 or 60 days), the authors stated that fecundability was significantly reduced (0–30 days postinfection, fecundability ratio = 0.2, 95% confidence interval: 0.03, 1.39; 0–60 days postinfection, fecundability

ratio = 0.82, 95% confidence interval: 0.47, 1.45). However, the confidence intervals for these findings crossed 1.0, so a statistical difference in fecundability between men with and without a recent SARS-CoV-2 infection could not be established. Taken together, the authors concluded that COVID-19 vaccination does not impair fertility in either men or women and that SARS-CoV-2 infection in men may be associated with a transient reduction in fertility.

We congratulate Wesselink et al. on this prospective cohort study using the PRESTO database. Their findings provide the best data available to date regarding the relationship between COVID-19 infection, COVID-19 vaccination, and fertility. The study is strengthened by its prospective nature; it is the first study to prospectively assess the impact of COVID-19 infection and vaccination on menstrual-cycle length and fertility. Its prospective nature reduces the risk of recall, selection, and ascertainment bias. Additionally, the study is the largest to date investigating the fertility implications of COVID-19 infection and vaccination. It includes a population that is more geographically and socioeconomically diverse than those in prior studies and captures individuals with no known history of infertility during the preconception window. Moreover, the rates of loss to follow-up are low and comparable in the vaccinated and unvaccinated groups, and the authors were able to adjust for potential socioeconomic, lifestyle, occupational, and reproductive confounders.

As with any nonrandomized study, the PRESTO database has the potential for residual confounding, particularly given the self-selection required for enrollment; those who choose to enter the study may be inherently different from those who do not. That being said, it is unlikely that this potential selection bias would affect the relationship between COVID-19 infection or vaccination and fertility. Although Wesselink et al. relied on self-reporting of vaccination status in their study (25), it is reassuring that prior studies have shown vaccination self-reporting to be highly accurate. The authors also relied on self-reporting of SARS-CoV-2 infection, which could have resulted in an underestimate of infection, leading to an underestimation of the impact of infection on fertility. Finally, although the study population is more diverse than in previously published reports on smaller cohorts in which the relationship between COVID-19 and fertility was investigated, the population remains less diverse than the US demographic distribution.

CONCLUDING REMARKS

To place this study in a broader context beyond the scope of the current pandemic, the ASRM COVID-19 Task Force is fully aligned with recent efforts to foster scientific research to address gaps in knowledge about safe and effective therapies and preventive measures for individuals contemplating pregnancy and during pregnancy. These efforts include 2 initiatives that predated the current pandemic: 1) a task force on research specific to pregnant and lactating women that was established by the 21st Century Cures Act in 2017 (26); and 2) the Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT)

project, which includes a multidisciplinary, international team with expertise in medicine, research, public policy, and ethics. The aim of PREVENT is to ensure that pregnant women and their offspring benefit from advances in vaccine technologies and biomedicine in the face of emerging and re-emerging pathogenic threats (27). The ASRM COVID-19 Task Force seeks to further support research aimed at the development of preventive and therapeutic measures to assist those contemplating pregnancy and who are pregnant during the current and/or future pandemics.

In summary, Wesselink et al. document in this prospective preconception study of more than 2,100 women that vaccination in the United States and Canada is not associated with any change in fecundity for either men or women. In view of the lack of biological plausibility that vaccination would adversely affect fertility, these findings are not surprising. The safety and efficacy of vaccination against SARS-CoV-2 infection support its use by the population at large. Given the increased morbidity and mortality associated with COVID-19 infection during pregnancy, vaccination is especially important for individuals who are contemplating pregnancy or already pregnant.

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