

Title: Vaccines and fertility: Why worry?

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Abbreviations: CDC, Centers for Disease Control and Prevention

Abstract

In this issue of the *Journal*, Wesselink et al. (Am J Epidemiol. XXXX;XXX(X):XXXX–XXXX) present findings that indicate that the COVID-19 vaccine does not cause any reduction in fertility in either men or women, while COVID-19 infection may reduce fertility temporarily among men. These are reassuring findings for those seeking pregnancy, clinicians, and the public. There was no scientific reason to be concerned about effects of the COVID-19 vaccine on fertility, so some of the psychological, ethical, and historical reasons for concern are discussed. These include perceptions of risk around “unnatural”, unusual, or dreaded outcomes; vaccine resistance as part of a social and political identity; and the tendency for moral panics to occur around women’s reproductive capacity. On this and other topics, there is a broad need for reproductive health to be better incorporated into clinical trials, and fertility research to advance in measurement and include a more diverse and global population.

Key words: COVID-19, vaccines, fertility, risk perception

In this issue of the *Journal*, Wesselink *et al.* (1) present findings that indicate that the COVID-19 vaccine does not cause any reduction in fertility in either men or women, while COVID-19 infection may reduce fertility temporarily among men. These are reassuring findings for those seeking pregnancy, clinicians, and the public, which is most protected when the widest range of people are vaccinated. They confirm that concerns about fertility should not restrict an important advance in public health.

Do we accept these results? The Wesselink study has several strengths, including a prospective design and detailed analysis that takes into account possible subgroup effects and alternative explanations. A minor concern might be that the censoring was informative, as loss to follow-up, stopping pregnancy attempt, and starting fertility treatment are treated equally in the analysis, though they have different implications for fertility. Overall, however, we can feel confident that, in this sample, there was no relationship between vaccination and infertility. The results are also consistent with available scientific knowledge, which does not suggest a mechanism for vaccine effects but does suggest some for COVID-19 infection (2).

A priori, there is no particular reason to be concerned about effects of the COVID-19 vaccine on fertility. Vaccines generally do not affect fertility, or affect them positively (3). The COVID-19 vaccine trials found no obvious effects on fertility or related parameters. However, trials cannot hypothesize every possible outcome. Patients sometimes notice differences that are invisible to researchers (4), and post-marketing surveillance detects rare outcomes (5). Fertility is an outcome for which degree of relevance varies substantially across the life course, and a reduction

in fertility is likely to go unnoticed by those not attempting to conceive. Examination of the scientific question is not unwarranted.

The limitations of this study are primarily in the study population, which is largely educated, higher-income, White, and based in the U.S. While there is no reason to think the biology of the vaccine differs due to these factors, they are strongly associated with age at pregnancy and thus fertility, as well as likelihood of vaccination (6). Factors relevant to vaccine effectiveness, such as comorbidities or predominant variants, could differ in the general population or other settings. Beyond this, the range of fertility experience in the cohort is limited on both ends, as the study excluded those trying to conceive for > 6 months or who were using or started fertility treatment. The most fertile are probably also underrepresented, as enrolling in a study will probably not be most people's first priority when choosing to have a baby, and a certain proportion who intended to enroll will become pregnant before they have the opportunity (though this is partially accounted for by using the survival model for left truncation). The finding of a reduction in fertility with COVID-19 infection has to be taken as tentative, given that COVID-19 infection was probably underestimated and those who were concerned enough and able to test for COVID-19 may have also differed in terms of health or behavior.

That new inventions lead to worries about fertility is almost a given. Negative effects on reproductive anatomy and fertility have been purported for trains (7), sewing machines, bicycles (8), air travel (9), and genetically modified food (10). Longstanding sexism makes women's fertility both overvalued and understudied, although in many of these cases scientific evidence is stronger for effects on male fertility (11), due to anatomy more vulnerable to external exposures.

The first concerns in moral panics about new technologies relate to children and women (12). Fertility has obvious links with these groups, and is deeply tied to moral, ethical, and religious principles. This may make judgments around fertility less rational and more value-based than those surrounding, say, kidney disease. In some parts of the world, polio eradication has been hampered by rumors that the polio vaccine might cause infertility, with the vaccine sometimes perceived to cause immodesty and being the subject of clergy fatwah (13, 14).

One interesting factor is the relative concern over vaccines compared to infection. It's arguable whether vaccination should even be considered a health risk when the alternative is almost always worse; COVID-19 infection has been found to cause effects on reproductive biology in males and females in several human and animal studies (15), but this fear did not encourage increased social distancing or isolation in young people (16). Human psychological quirks over-rate risks due to actively committed, out of the ordinary (most days people are not injected with a new vaccine), or "unnatural" acts with dreaded consequences (infertility) relative to those that are omitted, usual, or natural, with common/minor outcomes (a few days in bed) (17-20). In some cases, a concrete health concern may be an excuse for avoiding something that causes anxiety for no conscious reason. Vaccines may trigger associations with pain inflicted and not understood in childhood (21, 22), making it easier to believe they have negative effects.

Pre-COVID, discussion around vaccine hesitancy focused on the fact that many vaccine-preventable diseases had become so rare that people were unaware of their severity (23).

However, a year of COVID restrictions and millions of deaths worldwide were not enough to overcome high perceived vaccine risk for some people. A degree of accurate risk perception

does come into play: on average, reproductive-aged adults are at lower risk for complications from COVID-19 than older people (24), and older age is a major predictor of vaccination.

However, a pre-COVID study found that older people were less likely than younger ones to accept the risk of a vaccine against a fatal influenza that caused a complete lockdown (25). The contradiction may represent the difference between a hypothetical and real situation, though influenza vaccination behavior has been found to be predicted by omission and naturalness bias expressed under hypothetical scenarios (26). COVID-19 vaccine resistance differs from this hypothetical in that it has been bolstered by social and broadcast media with no responsibility to be accurate, and stoked by political and social tensions (27).

Vaccine or COVID-19 effects are generally understood to be biological rather than behavioral – Wesseling *et al.* provide references for reduction in fertility due to biological effects on sperm production, but behavioral effects (or residual confounding after control for intercourse frequency) are equally likely. Pandemics have caused birth shocks throughout history (28), due to a combination of deaths, sickness, economics, behavioral changes such as social distancing, and effects on fertility and fetal loss (29, 30). The initial blog post which suggested an effect of the vaccines focused on a protein in the endometrium rather than the chance that tiredness, headache, and muscle pain might limit sexual behavior for a few days, surely the most common vaccine-related fertility-reducing scenario. Most likely, because people can much more accurately assess this second risk, they become more concerned about the first, which featured details of uterine biology generally unknown to those who are not reproductive biologists.

Encouraging vaccine resistance is easier when the proposed adverse effects are subtle, long-term, and vaguely scientific-sounding, and therefore unrefutable.

The COVID-19 pandemic has provided a brutal illustration of the importance of scientific communication. The CDC and other health organizations have been criticized for unclear messaging, including changes in recommendations around masking and quarantine periods. Scientists', including epidemiologists', concerns about expressing uncertainty, or the alternative wish to forcefully communicate the weight of the evidence, can lead them to be too wishy-washy or too dismissive of genuine concerns, whether substantiated by evidence or not. Ironically, scientists need to acknowledge the expertise of those who study the best methods of communicating scientific uncertainty, as well as encourage more research in the best way to convey the state of public health knowledge when it is changing daily (31).

As variants spread and vaccines are modified to respond, continued surveillance will be necessary. Rigorous analyses are still needed on the question of whether menstrual cycle function is disrupted or other uterine bleeding is caused by the vaccine, as the study designs of the reports to date leave these as open questions. The major data gaps here are not so much for this individual vaccine or outcome, but for fertility and reproductive health in general. One reason for lack of evidence is the exclusion of pregnant women and those intending to conceive from vaccine and other trials. Both for this topic and fertility research more generally, populations of color and from outside the US and Western Europe are underrepresented. These groups are on average less likely to access assisted reproductive technologies (32, 33), and thus are less likely to be included in clinic-based fertility research. They are more likely meet the clinical definition of infertility without considering themselves infertile (34), thus minimizing their inclusion in survey-based research. Fertility is also a difficult endpoint, as it is only a theoretical outcome unless someone is having unprotected sex, making it tricky to identify the

population at risk. Subclinical markers of fertility exist, but sperm characteristics, menstrual cycle parameters, and subtle hormonal shifts are difficult to operationalize and have weak correlations with hard endpoints like livebirth (35, 36). Epidemiologists' strengths in rigorous study design and measurement mean they have a key role in furthering public health in this area. Ultimately, however, the COVID-19 vaccine is just another safe technology that reduces morbidity and mortality, and messaging and misinformation are a bigger threat to its uptake than the unlikely potential to cause infertility.

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