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Scientific Evidence Supporting Coronavirus Disease 2019 (COVID-19) Vaccine Efficacy and Safety in People Planning to Conceive or Who Are Pregnant or Lactating

Guillermina Girardi, PhD, **Andrew A. Bremer, MD, PhD**

Pregnancy and Perinatology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA.

Abstract

Three coronavirus disease 2019 (COVID-19) vaccines have been authorized for use in the United States; specifically, the Pfizer–BioNTech, Moderna, and Johnson & Johnson–Janssen COVID-19 vaccines were granted an emergency use authorization (EUA) by the U.S. Food and Drug Administration in early 2021. Vaccination coverage and intent among adults are lowest among those aged 18–39 years and among females in particular. In females of reproductive age, enthusiasm for receiving a COVID-19 vaccine may be negatively affected by claims currently circulating widely on diverse social media platforms regarding SARS-CoV-2 vaccines adversely affecting fertility and pregnancy. Yet it is important to note that these claims are anecdotal in nature and not supported by the available scientific evidence. It is also imperative that the effects of COVID-19 vaccine on reproductive health are clarified. Herein, we discuss the existing scientific data supporting COVID-19 vaccine safety and efficacy in people that are planning to conceive or who are pregnant or lactating, and highlight the importance of COVID-19 vaccination in females of reproductive age.

Prècis

The existing scientific data support coronavirus disease 2019 (COVID-19) vaccine safety and efficacy in people that are planning to conceive or who are pregnant or lactating.

Three COVID-19 vaccines are authorized for use in the United States; specifically, the Pfizer–BioNTech, Moderna, and Johnson & Johnson–Janssen COVID-19 vaccines were granted an emergency use authorization (EUA) by the US Food and Drug Administration (FDA) in early 2021. The Pfizer–BioNTech COVID-19 vaccine subsequently received full approval by the FDA on August 23, 2021 (1).

Corresponding author: Guillermina Girardi, Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD, USA, Guillermina.girardi@nih.gov.

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To achieve herd immunity, and thus reduce the spread and mutation of the virus, approximately two thirds of the population needs to be vaccinated (2, 3). Unfortunately, COVID-19 vaccination programs globally report a high level of vaccination hesitancy (4). The World Health Organization (WHO) defines vaccination hesitancy as a delay or total refusal to receive a vaccine independent of availability of vaccines (5). Since April 19, 2021, all persons aged 16 years and older in the US are eligible for COVID-19 vaccination. Interestingly, vaccination coverage and intent among adults are lowest among those aged 18–39 years. While COVID-19 vaccines are authorized with strict standards set by the FDA prior to approval, concerns about vaccine safety and effectiveness are commonly cited barriers to vaccination by younger adults (6). There is an important gender gap in COVID-19 vaccination rates. Specifically, young females have a lower vaccination rate than young males.

In females of reproductive ages, enthusiasm for receiving a COVID-19 vaccine may be negatively affected by claims currently circulating widely on diverse social media platforms regarding SARS-CoV-2 vaccines adversely affecting fertility and pregnancy (7–9). It is of great concern that these claims, anecdotal in nature and relying only on personal observation are still circulating online, despite not being supported by evidence. To highlight the importance of this misinformation, the US Surgeon General recently described the rise of false information around COVID-19 vaccines as an “urgent threat” that continues to put “lives at risk” and prolong the pandemic (10).

In this commentary, we discuss the existing scientific data supporting the safety and efficacy of COVID-19 vaccines in females of reproductive age.

COVID-19 VACCINES: MENSTRUATION AND FERTILITY

Numerous media reports question whether COVID-19 vaccines cause menstrual cycle problems. However, to date, the US Vaccine Adverse Event Reporting System (VAERS) has recorded only a small number of minor and transient menstrual-related adverse events among the more than 72 million females who have been vaccinated against SARS-CoV-2 (11). Interestingly, similar concerns were also raised with the human papillomavirus (HPV) vaccine and later proven to be inaccurate (12).

A mechanism based on the similarity between the SARS-CoV-2 spike protein and syncytin-1, a protein involved in implantation and placentation, was proposed on social media to create concern about potential adverse effects of COVID-19 vaccines on fertility (13). However, this hypothetical immune cross-reactivity that could result in implantation failure has proven erroneous as the two proteins only share a sequence of four amino acids. Furthermore, it has been demonstrated that antibodies formed after a natural SARS-CoV-2 infection or COVID-19 vaccination do not bind to syncytin (8). Additionally, if cross-reactivity did occur, it would also cause sterility by natural antibodies produced by the illness itself and would have a prolonged effect; however, this also has not been reported.

Another inaccurate theory for potential adverse outcomes following vaccination is that mRNA from the COVID-19 vaccine accumulates in the ovaries. This erroneous claim was

based on a study in which rats received a much higher dose of a COVID-19 vaccine than that given to humans and lipids from the vaccine shell accumulated in the ovaries. (14). Other vaccine components and mRNA from the vaccine did not concentrate in the rat ovary. Importantly, a recent report from the European Medicine Agencies, suggests a low biodistribution of mRNA is found in the ovaries and testes after SARS-CoV-2-based mRNA vaccination (15).

Moreover, an additional study in rats demonstrated that there were no effects of the COVID-19 mRNA vaccine on female mating performance, fertility, or any ovarian or uterine parameters (16). In addition, this study also showed that embryo-fetal or postnatal survival, growth, and development in the offspring through the end of lactation was not affected by COVID-19 vaccine administration (16).

A recent study in humans found that ovarian follicular function is also unaffected by SARS-CoV-2 infection or the Pfizer–BioNTech vaccine (17). These observations resulted from a clinical trial studying anti-SARS-CoV-2 antibodies in follicular fluid and spermatic fluid in patients undergoing in vitro fertilization (18).

Similarly, in a study of individuals attempting conception using frozen embryo transfer, the implantation rates were compared among Pfizer–BioNTech vaccine-induced SARS-CoV-2 seropositive and Moderna vaccine-induced SARS-CoV-2 seropositive (reactive vaccine), SARS-CoV-2 seropositive (reactive infection), and seronegative individuals (non-reactive). The authors found that implantation rates documented by serum hCG, sustained implantation rates and visualization of gestational sacs were not different among the three groups (19). This study was important in that it also demonstrated that the presence of antibodies to the SARS-CoV-2 spike protein, whether after vaccination or SARS-CoV-2 infection, does not affect embryo implantation or early pregnancy development (19).

Together, the studies in humans and animals, indicate that there is no scientific evidence that the COVID-19 vaccine has deleterious effects on female fertility.

COVID-19 VACCINES IN PREGNANCY

Ethical concerns regarding testing vaccines in pregnant and lactating persons have been expressed for a long time, frequently resulting in the exclusion of these populations from clinical trials, even if they were willing to give informed consent. The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established as part of the 21st Century Cures Act (20). Since its formation in 2016, PRGLAC has advised the Secretary of Health and Human Services (HHS) regarding the need for knowledge and research on safe and effective therapies for pregnant and lactating persons (21). Although not anticipated at the time that PRGLAC was formed, the COVID-19 pandemic highlights why the recommendations of this Task Force should be implemented and that pregnant and lactating individuals should be protected ‘through’ research rather than ‘from’ research (22).

There is currently no biological reason to expect that mRNA COVID-19 vaccination would have adverse effects either preconceptionally or during pregnancy and while lactating. It is also now well documented that SARS-CoV-2 infection during pregnancy is associated

with severe illness with increased risk of intensive care unit (ICU) admission, death, and adverse pregnancy outcomes (23–25). According to recent data released by the National Health Service in the United Kingdom, nearly 20 percent of the most critically ill patients with COVID-19 in England are unvaccinated pregnant individuals (26). A similar pattern is currently seen in the USA (27).

Viral infections can be more severe in pregnant individuals in part because the immune system is directed towards fetal tolerance. In addition, SARS-CoV-2 is targeted to the lungs and the cardiovascular system, which are physiologically stressed during pregnancy. Moreover, pregnancy and SAR-Co-V-2 infection are associated with a procoagulant effect, increasing the likelihood of thrombosis (25).

RT-PCR and RNAscope data demonstrate the presence of SARS-CoV-2 in placental tissue from infected mothers (28, 29). Additionally, expression of the receptor for the SARS-CoV-2 virus, angiotensin-converting enzyme 2 (ACE2), has been detected in the placenta throughout pregnancy by immunohistochemistry in affected individuals (30). Thus, SARS-CoV-2 infection of the maternal placental surface may induce acute or chronic placental insufficiency leading to pregnancy complications. As such, given that data suggest that SARS-CoV-2 reaches the placenta and that adverse pregnancy outcomes have been reported in infected pregnant individuals (31, 32), immunizing reproductive-age females before and during pregnancy may have a large public health benefit.

A recent study also showed that COVID-19 vaccination during pregnancy is associated with lower odds of severe or critical coronavirus disease 2019 (COVID-19) in pregnant patients during the Delta-predominant surge (33). Another recent study reported that vaccinated pregnant individuals were less likely than unvaccinated pregnant patients to experience COVID-19, and that COVID-19 vaccination during pregnancy was not associated with increased pregnancy or delivery complications (34). These studies thus highlight the potential benefits of the SARS-CoV-2 vaccine in preventing severe or critical illness and adverse pregnancy outcomes.

COVID-19 vaccine hesitancy among individuals who are pregnant or planning to conceive may unfortunately be facilitated by false reports associating vaccination with pregnancy loss. While miscarriages have been reported to vaccine-monitoring venues, including the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card scheme in the United Kingdom (UK) and the VAERS in the US, it needs to be taken into consideration that: (i) these databases reflect self-reported measures; and (ii) for each reported pregnancy loss it was not scientifically proven that miscarriage was directly caused by the vaccine. Miscarriages are fairly common in the general population; in fact, it is estimated that as many as 26% of all pregnancies end in miscarriage. The self-reported rate of miscarriage in people who received the COVID-19 vaccine from these established reporting systems is consistent with the rate expected in the general population (35).

A large study including 2,456 pregnant persons who received an mRNA COVID-19 vaccine preconception or prior to 20 weeks' gestation conducted by the Centers for Disease Control and Prevention (CDC) found that vaccination during preconception or during pregnancy

is not associated with an increased risk of spontaneous abortion (36). Moreover, a recent study using the Vaccine Safety Datalink found that spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination in the prior 28 days compared with ongoing pregnancies (37). These findings thus suggest that mRNA COVID-19 vaccines during pregnancy are safe.

Another concern that might prevent pregnant people from getting vaccinated for COVID-19 is the potential development of fever after the vaccination injections, particularly during the first trimester during which maternal high fever has been associated with teratogenicity (38). However, a large prospective cohort study in the US found that vaccination reactions after the Pfizer–BioNTech or Moderna mRNA-1273 vaccines consisted only of mild fever, similar among individuals who were pregnant, lactating, or planning pregnancy compared with non-pregnant individuals (39).

Furthermore, studies in animals suggest that there are no safety concerns associated with the COVID-19 vaccines from Pfizer–BioNTech and Moderna on pregnancy outcomes. Specifically, a report of developmental and reproductive toxicology studies on the Pfizer–BioNTech vaccine in rats, showing no adverse effects, was recently sent to the FDA (40), and the Vaccines and Related Biological Products Advisory Committee (VRBPAC) briefing documents showed no abnormalities were found in the developmental and perinatal and postnatal studies.

Moreover, histological examination of placentas in individuals that received COVID-19 vaccination showed no increased incidence of decidual arteriopathy, fetal vascular malperfusion, low-grade chronic villitis, or chronic histiocytic intervillositis compared with unvaccinated individuals (41).

Vaccines that use viral vectors platforms, such as the one used in the J&J–Janssen COVID-19 vaccine, have also been given to pregnant people in all trimesters of pregnancy, including in a large-scale Ebola vaccination trial. Importantly, no adverse pregnancy and neonatal outcomes have been observed with vaccination in these trials as well (42).

The CDC also recently released the first US data on the safety of receiving an mRNA COVID-19 vaccine during pregnancy. This report analyzed pregnancy outcomes including pregnancy loss (spontaneous abortion and stillbirth) and neonatal outcomes (preterm birth, congenital anomalies, small size for gestational age, and neonatal death) from several safety monitoring systems (43). Importantly, the studies did not find any safety concerns for pregnant people who were vaccinated or their offspring. Several studies also demonstrate the efficient transfer of SARS-CoV-2 antibodies to the fetus following maternal vaccination (44–46). mRNA COVID-19 vaccines in pregnant individuals lead to maternal antibody production as early as 5 days after the first vaccination dose and transplacental transfer of passive immunity to the neonate as early as 16 days after the first vaccination dose (44). Importantly, these data suggest that COVID-19 vaccination during pregnancy might help protect fetuses and neonates against COVID-19.

COVID-19 VACCINATION WHILE LACTATING AND BREASTFEEDING

COVID-19 vaccination is recommended for people who are lactating and breastfeeding (47). Importantly for the infant, breastfeeding people who have received mRNA COVID-19 vaccines showed the presence of antibodies in their breastmilk (48, 49). One of these studies found robust secretion of SARS-CoV-2 specific IgA and IgG antibodies in breast milk for 6 weeks after vaccination (49). Furthermore, IgA secretion was detected as early as 2 weeks after vaccination followed by an increase in IgG after 4 weeks (a week after the second vaccine). Antibodies detected in breast milk of mRNA COVID-19 vaccinated individuals also showed strong neutralizing effects (49), suggesting a potential protective effect against infection in the infant. Interestingly, a recent study in individuals who reported to be breastfeeding at the time of COVID-19 vaccination found that the anti-SARS-CoV-2 IgG and IGM concentrations in human milk was significantly higher in mothers that were breastfeeding for 24 months compared to mothers with breastfeeding periods of less than 24 months (50).

Additionally, no serious adverse events were reported by 180 breastfeeding individuals receiving either the Pfizer or Moderna vaccine. Mothers and their infants experienced none to very mild side effects after receiving mRNA COVID-19 vaccines according to this study (51). These data are thus reassuring regarding the safety of vaccination in breastfeeding individuals and their breastfed children with either of the mRNA COVID-19 vaccines.

Conclusion

Vaccine hesitancy in reproductive-aged females is concerning and has likely resulted from the spread of misinformation on social media platforms suggesting that COVID-19 vaccines may cause sterility or pregnancy complications. However, the scientific data suggest no evidence that the COVID-19 vaccines currently used in the US have any negative effects on female reproductive health. Recently, the CDC recommended that any American who is pregnant, planning to become pregnant, or currently breastfeeding get vaccinated against the COVID-19 as soon as possible (52). These recommendations are aligned with those from professional medical organizations including the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) (53). Importantly, the increased COVID-19 severity and risk of death and adverse pregnancy outcomes observed with SRAS-CoV-2 infection during pregnancy (23–29) and the growing evidence about the safety and effectiveness of COVID-19 vaccination during pregnancy both suggest that the benefits of receiving a COVID-19 vaccine during pregnancy would outweigh any potential adverse effects on the pregnant individual or the fetus. As such, in a collaborative effort, physicians and other health care professionals should reassure all individuals – especially those who are pregnant, lactating, or planning to conceive – that vaccination to COVID-19 is safe and moreover has great benefits in preventing infection to themselves and their offspring.

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