



Effects and safety of COVID-19 vaccination on assisted reproductive technology and pregnancy: A comprehensive review and joint statements of the KSRM, the KSRI, and the KOSAR

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Humanity is in the midst of the coronavirus disease 2019 (COVID-19) pandemic, and vaccines—including mRNA vaccines—have been developed at an unprecedented speed. It is necessary to develop guidelines for vaccination for people undergoing treatment with assisted reproductive technology (ART) and for pregnancy-related situations based on the extant laboratory and clinical data. COVID-19 vaccines do not appear to adversely affect gametes, embryos, or implantation; therefore, active vaccination is recommended for women or men who are preparing for ART. The use of intravenous immunoglobulin G (IVIg) for the treatment of immune-related infertility is unlikely to impact the effectiveness of the vaccines, so COVID-19 vaccines can be administered around ART cycles in which IVIg is scheduled. Pregnant women have been proven to be at risk of severe maternal and neonatal complications from COVID-19. It does not appear that COVID-19 vaccines harm pregnant women or fetuses; instead, they have been observed to deliver antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the fetus. Accordingly, it is recommended that pregnant women receive COVID-19 vaccination. There is no rationale for adverse effects, or clinical cases of adverse reactions, in mothers or neonates after COVID-19 vaccination in lactating women. Instead, antibodies to SARS-CoV-2 can be delivered through breast milk. Therefore, breastfeeding mothers should consider vaccination. In summary, active administration of COVID-19 vaccines will help ensure the safe implementation of ART, pregnancy, and breastfeeding.

Keywords: Assisted reproductive technology; COVID-19; Lactation; Pregnancy; Vaccination

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Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is mediated through angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) on the host cell surface. COVID-19 can be fatal due to systemic inflammation accompanied by the secretion of large amounts of inflammatory cytokines [1]. Since human reproduction, from gametogenesis to delivery, is a dynamic process involving multiple steps of endocrine and immuno-

logical signaling [2-4], and ACE2 and TMPRSS2 are also expressed in various cells of the human reproductive system [5-7], concerns have been raised about the possibility that COVID-19 might have adverse effects on human reproduction. No direct or permanent detrimental effects on the female reproductive system have yet been reported in women infected with COVID-19. However, orchitis and impaired spermatogenesis have been reported in male COVID-19 patients [8].

All the currently approved COVID-19 vaccines act by inducing antibodies against the spike protein, which interacts with ACE2 on the cell surface, and some people have expressed concerns about the possibility that the spike protein might exert harmful effects as a pathogenic protein or a toxin. Due to a lack of information about the possible adverse effects of the COVID-19 vaccines on human reproduction, some couples seeking care at infertility clinics hesitate to receive vaccination [9]. As will be discussed in this review, COVID-19 vaccines have been developed and applied in clinical practice at an unprecedented speed, and the clinical evidence for many questions related to human reproduction is still insufficient. Vaccination is crucial for overcoming the COVID-19 pandemic, and it is very important to provide appropriate guidance for men and women who are preparing for pregnancy or lactating. Healthcare providers working in the field of human reproduction must be well informed on the latest recommendations and research about COVID-19 vaccines. According to this vision, the joint committee members of the Korean Society for Reproductive Immunology, the Korean Society for Reproductive Medicine, and the Korean Society for Assisted Reproduction formed a working group and thoroughly reviewed the representative international guidelines and statements on COVID-19 vaccination and relevant clinical and theoretical evidence about human reproduction [10-13]. Through this process, we provide statements on COVID-19 vaccination in the clinical context of assisted reproductive technologies (ARTs), pregnancy, and lactation.

Should women and men planning to conceive, including ART cycles, receive COVID-19 vaccination?

Since none of the currently approved COVID-19 vaccines, including mRNA vaccines and adenovirus vector vaccines, not contain live viruses, there is no theoretical risk of vaccine-related infection. According to a fact sheet published by the United States Food and Drug Administration, animal studies have demonstrated no increased adverse effects on reproductive outcomes, such as female fertility, embryonic-fetal development, and the postnatal prognosis when mRNA COVID-19 vaccines were delivered before the mating period or during early or late gestation [14]. A recent study showed that mRNA COVID-19 vaccines did not affect subsequent *in vitro* fer-

tilization (IVF) cycle performance from 7 to 85 days after receiving the second vaccine dose, including the number of retrieved mature oocytes, the number of top-quality embryos, and sperm parameters [15]. Although it was only a small-sized study published before being peer-reviewed, a subsequent study also showed the same results [16]. Another study reported no change in sperm parameters before, after, or during COVID-19 vaccination [17]. Accordingly, joint guidance from the International Federation of Fertility Societies and the European Society of Human Reproduction and Embryology advises women who are trying to conceive but are not yet pregnant, that they have the option to “proceed with efforts at conception” and to “seek a COVID-19 vaccination as soon as possible” [11], and the American Society for Reproductive Medicine COVID-19 Task Force re-confirmed their statement, recommending that “there is no reason to delay pregnancy attempts because of vaccination administration or to defer treatment until the second dose has been administered” [12,13].

However, without a clear explanation of the relationship between IVF treatment and the immune reaction from COVID-19 vaccination, clinicians face limitations in counseling patients attempting IVF treatment about the optimal timing of COVID-19 vaccination. In particular, real-world data have yet to be reported for emergent ART cases, such as fertility preservation (FP) just before gonadotoxic treatment or in patients with severe ovarian insufficiency (OI). IVF cycles can usually be electively planned according to patients' status, and scheduling the timing of vaccination is not difficult. However, in emergent cases, physicians may need to decide to start the ART cycle between the first and second vaccine doses. There is a possible concern about immunological changes resulting from elevated hormonal levels during ART cycles; however, the elevation of estradiol levels is not extremely high in most cases of FP or OI. The embryo transfer schedule is separate from oocyte retrieval in most FP cases, and it can also be delayed in OI cases by embryo cryopreservation. According to animal and human data suggesting no detrimental effects on gametes, physicians should not hesitate to start FP and freeze-all cycles (i.e., cryopreservation of all retrieved oocytes or all fertilized embryos), regardless of the vaccination schedule. The only recommendation is to avoid vaccination 3 days before or after an elective fertility-related procedure such as oocyte retrieval [16]. There is still insufficient evidence as to whether there should be a gap of more than 3 days between the vaccine and the procedure. However, there is a possibility of adverse effects such as fever and generalized pain due to the initial immune response after vaccination, and it may be difficult to differentiate whether side effects are due to vaccination or ART procedures. For this reason, it is recommended to have an interval of approximately 3 days, which does not affect the overall ART schedule.

(1) All women and men planning to conceive are recommended to receive COVID-19 vaccination. (2) Based on current evidence, COVID-19 vaccination does not adversely affect fertility in women or men. (3) Scheduling the ART cycle with consideration of COVID-19 vaccination is helpful when counseling couples visiting infertility clinics. (4) In emergent cases, such as FP just before gonadotoxic treatment, the ART cycle can be started during vaccination after consultation with clinicians.

Should women planning to undergo immunomodulatory or immunosuppressant treatment during the ART cycle receive the COVID-19 vaccine?

Immunomodulatory or immunosuppressant agents are considered in patients with repeated implantation failure or recurrent pregnancy loss with possible immunological etiologies [18,19]. Women on immunomodulatory or immunosuppressant therapies such as anti-tumor necrosis factor agents and high-dose steroids for autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, and poorly controlled asthma) generally visit infertility clinics to have a baby. Although these cases are not common [20,21], physicians can be asked about the possibility of interference between immunomodulatory or immunosuppressant therapies and COVID-19 vaccination during ART procedures.

Antibody-containing blood products, such as intravenous immunoglobulin G (IVIG), interfere with the immune response to some live attenuated vaccines such as measles-mumps-rubella and varicella, but not with the response to inactivated or toxoid vaccines. For inactivated vaccines, administration simultaneously with IVIG injection, or at any time interval before or after IVIG treatment, is allowed [22]. Although no clinical data have yet been published about immune interference between the COVID-19 vaccines and IVIG, mRNA COVID-19 vaccination is theoretically allowed based on these previous data.

Although inactivated non-live vaccines are recommended to be administered to immunosuppressed patients, as for healthy individuals, sometimes a higher dosage or more frequent booster shots may be required [23]. In terms of COVID-19, immunosuppressed patients due to disease or treatment are defined as a clinically vulnerable group and recommended to complete the vaccination schedule as soon as possible [24]. In addition, early and frequent boosters are considered for immunosuppressed individuals according to the results of the OCTAVE trial, which reported failed or reduced generation of protective antibodies after the completion of two doses of COVID-19 vaccines in immunocompromised patients [25]. In this context, the use of immunosuppressive agents such as high doses of

steroids or tacrolimus only for the purposes of ART must be reconsidered in the era of the COVID-19 pandemic.

(1) Theoretically, the administration of IVIG does not interfere with the immune response to mRNA COVID-19 vaccines. (2) Based on current evidence, IVIG administration can be performed at any time during the COVID-19 vaccination schedule. (3) Patients receiving immunosuppressive treatment are recommended to receive a booster shot of the COVID-19 vaccine due to reduced generation of protective antibodies after two vaccine doses. (4) It is not recommended to use immunosuppressants solely for ART without other appropriate indications in the COVID-19 pandemic era.

Is COVID-19 vaccination safe for pregnant women?

Pregnant women have been reported to have a higher risk of developing severe illness from COVID-19 than non-pregnant women. In pregnant women infected with COVID-19, higher rates of maternal complications (e.g., mortality, need for intensive care unit care, mechanical ventilation, cesarean section, preterm delivery, and pre-eclampsia) have been reported, and neonatal and perinatal mortality and morbidity also appear to increase [26-29]. Although very rare, case reports of vertical transmission in the first trimester or third trimester of pregnancy have been reported [30,31]. To protect the vulnerable population of pregnant women, the safety and efficacy of COVID-19 vaccination in pregnant women should be established. Pregnant and lactating women were excluded from the initial clinical trials of COVID-19 vaccines due to safety and liability concerns. To overcome these limitations, clinical trials on the safety of the COVID-19 vaccine in pregnant women are currently underway [32]. However, until the results of these studies are published, clinical judgments must be made based on the previous results of existing vaccines for other viral diseases, animal experiments, and a small number of clinical reports.

It has been reported that the existing mRNA vaccines against influenza virus, rabies virus, and Zika virus are safe during pregnancy and have good immunogenicity profiles [33-35]. Animal developmental and reproductive toxicology studies on mRNA or adenovirus vector vaccines for COVID-19 reported that there were no adverse effects on fertility, maintenance of pregnancy, or embryonic and fetal development [36,37].

In clinical studies of mRNA vaccines or adenovirus vector vaccines against COVID-19, some female participants unintentionally became pregnant. In this minority of women, the miscarriage rates did not differ from those in the placebo group. Therefore, the vaccines do not appear to have a detrimental effect in early pregnancy [38]. When COVID-19-vaccinated pregnant women delivered, placental

examinations showed a similar incidence of decidual arteriopathy, fetal vascular malperfusion, low-grade chronic villitis, or chronic histiocytic inter-villositis as in women who were not vaccinated. This indicates that there is no evidence of a vaccine-derived breakdown in maternal immunologic tolerance to the fetal tissue [39].

The United States Centers for Disease Control and Prevention developed a smartphone-based active-surveillance system (“V-safe”) for the COVID-19 vaccination program. This system allows pregnant women to voluntarily report adverse events after COVID-19 mRNA vaccination. A recent report found no serious vaccine-related adverse events during pregnancy in 35,691 participants [40].

A study found that COVID-19 mRNA vaccines evoked robust humoral immunity in pregnant and lactating women, and the immunogenicity and reactogenicity of vaccination were similar to those observed in non-pregnant women [41]. After vaccination, immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike protein were observed to cross the placental barrier and approach maternal titers in the fetus within 15 days following the first dose [41,42]. These results support the placental transfer of protective immunoglobulins to neonates by COVID-19 vaccination.

(1) Pregnant women are at increased risk of severe maternal and neonatal complications if they are infected with COVID-19. (2) Pregnant women are recommended to receive COVID-19 vaccination. (3) Based on current evidence, COVID-19 vaccination does not adversely affect pregnancy and neonatal outcomes. (4) COVID-19 vaccination during pregnancy may have a protective effect on the fetus by delivering antiviral immunoglobulins via the placenta.

Should lactating women be vaccinated against COVID-19?

An analysis of postvaccination milk samples from women who received mRNA vaccines detected no or little vaccine mRNA was detected [43,44]. DNA sequences for the S protein delivered into cells through adenovirus vector vaccines are transcribed into mRNA, which is translated into the viral S protein. Since this process is similar to that of mRNA vaccines, it can be inferred that adenovirus vector vaccines will theoretically have the same stability as mRNA vaccines.

In breastfeeding women who received the mRNA vaccine, the maternal serum antibody titer was equivalent to that of non-lactating women [45]. After the first dose, anti-spike immunoglobulin A (IgA) and IgG levels in breast milk increased after 1 week. This increase has been reported to persist for more than 6 weeks after the second dose, and the positive effect of delivering antibodies to nursing infants for up to 80 days is likely to be maintained [46–48]. In a study comparing two doses of the Pfizer-BioNTech or Moderna vaccine (mRNA vaccines) with a single dose of the Astra-Zeneca (adenovi-

rus-vector vaccine), both IgA and IgG were observed in breast milk regardless of which commercial vaccine was administered [49]. In contrast, in two studies reported to date, anti-spike IgA and IgG antibodies were not detected in the plasma of infants after their mothers completed two doses of mRNA vaccine [50,51].

In an analysis of maternal interviews and questionnaires about side effects in nursing women who had completed two doses of the mRNA vaccine, some women reported decreased milk supply but returned to normal after 72 hours without any intervention [52]. The study also reported that 4%–8% of women described changes in the color of their milk. In an online survey of 4,455 breastfeeding mothers who received mRNA vaccines, 6% reported a decrease in milk supply, whereas 3.9% reported an increase in milk supply [53]. About 7% of mothers reported adverse effects in their breastfed infants. The most common events were irritability and sleep disturbances of infants (3%). In a cohort study of 180 nursing women who received mRNA vaccines, some reported similar side effects, including irritability in about 10% of infants and poor sleep in about 8% [52]. However, it is unclear whether these common symptoms are directly related to maternal vaccination, and until now, no serious adverse reactions have been reported in infants of breastfeeding mothers vaccinated against COVID-19 [47,51].

(1) Current evidence suggests that COVID-19 vaccination will not harm lactating women or breastfeeding infants. (2) When a lactating woman is vaccinated against COVID-19, antibodies may be secreted in breast milk and delivered to infants to provide protective effects. (3) COVID-19 vaccination is recommended for women who are breastfeeding or planning to start, as the currently known possible benefits outweigh the theoretical risks.

Conclusion

Based on the evidence to date, COVID-19 vaccines do not appear to have detrimental effects on human reproduction, including gametes, embryos, or implantation. Through these observations and analyses of causation, it is recommended that women or men who are preparing for ART be actively vaccinated. The use of IVIG for the treatment of infertility or recurrent miscarriage in patients with possible immune problems is theoretically unlikely to impact the effectiveness of the vaccine, and COVID-19 vaccines can be administered in an ART cycle in which IVIG is scheduled. COVID-19 vaccines do not appear to adversely affect pregnant women or neonates; instead, they deliver antibodies against SARS-CoV-2 to the fetus. Therefore, it is recommended that pregnant women actively take steps to receive the COVID-19 vaccine. When lactating women are infected with COVID-19, their baby can also be exposed to infection, whereas if lactating women are vaccinated against COVID-19, protective anti-

bodies to SARS-CoV-2 can be delivered to the baby via lactation without major adverse effects. Therefore, mothers who are breastfeeding need to consider COVID-19 vaccination. Active COVID-19 vaccination in the reproductive-age population will ensure safe ART, pregnancy, and breastfeeding.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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