





# The Importance of Female Reproductive Changes in COVID-19 and Vaccine Administration: A Narrative Review

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## ABSTRACT

The COVID-19 pandemic has disrupted people's lives all over the world, and vaccination is one of the best ways to eradicate this pandemic and save people's lives. Despite this, vaccines have many known and unknown side effects like fever, fatigue, headache, etc. Fertility is an important aspect of human life, but there are too many concerns about its relationship with COVID-19 and its vaccines. Women are complaining of menstrual irregularities like postmenopausal bleeding, heavy menstrual bleeding, polymenorrhea and fertility concerns after receiving the second dose of the COVID-19 vaccine. The immunologic reactions between vaccine ingredients and the immune system of the body seem to be responsible for this global issue. Angiotensin-converting enzyme 2 (ACE2) and Basigin (BSG) are the receptors for SARS-COV-2. ACE2 is expressed in the human respiratory system, kidney, vagina, uterus and particularly widely in the ovaries, and BSG is expressed in the uterus, ovary stroma and granulosa cells. Therefore, SARS-COV-2 can invade the target cells by attachment to ACE2 and BSG and modulate their expression, and through these probable mechanisms, it can disturb female reproduction and menstruation. According to this accumulated evidence, in this study we aimed at summarizing the recent studies with a focus on probable mechanisms by which SARS-COV-2 and COVID-19 vaccines affect menstruation irregularities and reproduction complications.

**Keywords:** Female Reproductive, Vaccine, Covid-19



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## Introduction

Nowadays, one of the most serious problems is COVID-19, an infectious disease that has become the main concern of physicians (1). It was accompanied by dangerous complications. Beforehand, it seemed it only affected the lungs, but with the advancement of information, it became apparent that the other organs would also suffer from complications (2). The infection can affect people of all ages, from infants to the elderly, who are immunocompromised (3). The most promising strategy for containing the pandemic is to develop vaccines to prevent SARS-CoV-2 infection. Preventative vaccination can minimize expenses and

play a key role in protecting people against viral illnesses in a cost-effective and long-term way (4).

As various side effects of COVID vaccines have been reported. One of the complaints was related to women's reproductive system problems, such as menstruation irregularities, an increased risk of miscarriage, and future infertility (5). Recent investigations have mentioned that SARS-CoV-2 enters the target cell through attachment to the angiotensin-converting enzyme 2 (ACE2) receptor (which is abundant in the ovaries, uterus, vagina, and placenta). This new virus is thought to disrupt female fertility by involving the ACE2 receptor, which

regulates follicular development and ovulation, endometrial tissue growth, and corpus luteum angiogenesis and degeneration (6, 7). However, there is currently no proof and no theoretical reason why any of the COVID-19 vaccinations might impair fertility, according to international consensus from numerous organizations advising on fertility (8). Herein, we are looking into whether COVID-19 vaccines have an impact on females' reproductive systems.

### **The menstrual changes related to the SARS-CoV-2 infection**

COVID-19 patients all over the world have experienced a variety of symptoms, such as fever, cough and myalgia (9). Additionally, menstrual cycle abnormalities were reported in some of the female COVID-19 patients. Reported changes in the menstrual cycle in childbearing-age female patients with COVID-19 mainly included an extended cycle length and a reduction of menstrual volume. However, in some of the patients, shortened cycle length and increased volume were reported. These changes were rare in the control group and more plausible in patients with multisystem dysfunction. Menstrual abnormalities were transient, and most of the patients, except for one, went back to normal menstrual status after discharge (10). According to the research carried out by Wilkins et al. on female patients with COVID-19 who were in reproductive age in Wuhan, China, only 15% of patients were reported to have amenorrhea or irregularities in their menstrual cycle. Also, 31.9% of patients were reported to have dysmenorrhea but menstruation-related information, including menstrual volumes, phase of menstrual cycle, menstrual status and dysmenorrhea history, that was collected from severe COVID-19 patients did not show a remarkable difference compared to non-severe ones. Despite these insignificant changes in menstruation, low ovarian reserve and irregularity in reproductive hormones in women with COVID-19 were indicated by low serum AMH and high T/PRL levels in comparison to healthy women (11). Nevertheless, the majority of women with COVID-19 included in the study had a regular menstrual cycle and showed no considerable abnormality in their menstruation (9, 10).

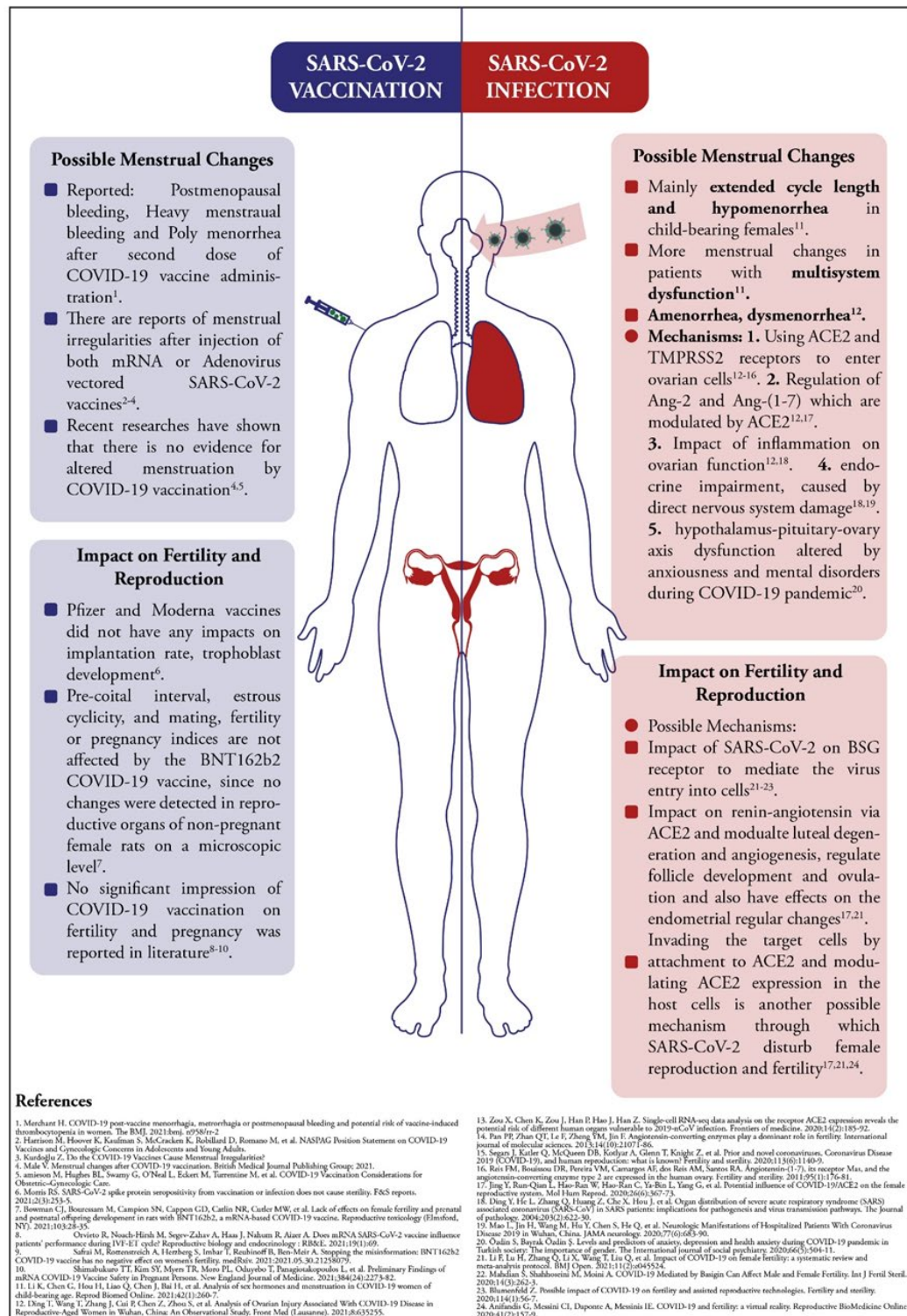
In one of the reported cases, a patient who had unprotected sex for over a year and didn't need hospitalization or active treatment in the acute phase of COVID-19 with common symptoms, was referred to a fertility clinic with irregular periods after 7 months. After investigation, a very low progesterone level and a high level of gonadotropins including follicle-stimulating hormone (FSH) and luteinizing hormone (LH) indicated premature ovarian insufficiency. Also, none of the common causes of this disease were observed in this patient (11). Thus, SARS-CoV-2 may cause impairment of ovarian function (11, 12).

Changes in menstrual cycle in patients with COVID-19 may occur due to different mechanisms, including: (i) the SARS-CoV-2 entry into ovarian cells via ACE2 receptor and TMPRSS2 and its local replication which leads to cytopathic effects (12-16), (ii) regulation of ovarian functions through Ang-2 and Ang-(1-7) which are modulated by ACE2 (12, 17), (iii) the impacts of immune system response and inflammation on ovarian function (12, 18), (iv) endocrine impairment, which is the most probable mechanism, caused by direct nervous system damage (18, 19) and the dysfunction of hypothalamus-pituitary-ovary (HPO) axis following anxiousness and mental disorders during COVID-19 pandemic (20) leading to an increase in LH level causing secondary ovulation dysfunction (12) (Figure 1).

At the end, further investigations are needed to evaluate the effects of SARS-CoV-2 on menstruation and its possible mechanisms.

### **Impact of COVID-19 on female fertility and reproduction**

The COVID-19 pandemic has had negative effects on many aspects of people's lives and health all over the world (21). Fertility is one of the most important parts of a human's life. There are concerns about its relationship with COVID-19, and some evidence demonstrates that COVID-19 may cause fertility problems through different mechanisms (22, 23). Basigin (BSG) is a transmembrane protein that is expressed in the uterus, ovary stroma and granulosa cells. It plays a role in follicle development, and has functions in female reproduction. BSG is an important receptor for SARS-CoV-2 that can mediate its entry into host cells. Through this strategy, COVID-19 may have adverse effects on reproduction and fertility (6, 24, 25). ACE2 is part of the renin-angiotensin system, which modulates Ang-(1-7) and Ang-2 levels (17). Ang-(1-7), Ang-2 and ACE2 modulate luteal degeneration and angiogenesis, regulate follicle development and ovulation, and also have effects on endometrial regular changes (6, 17). ACE2 is expressed in the human respiratory system, kidney, vagina, uterus and particularly widely in the ovaries. Also, ACE2 is present in oocytes, granulosa cells and stroma cells in immature rat ovaries (6, 17, 26). Therefore, invading the target cells by attachment to ACE2 and modulating ACE2 expression in the host cells is another possible mechanism through which SARS-CoV-2 disturbs female reproduction and fertility (6, 17, 22). Nevertheless, the magnitude of the association between female fertility and COVID-19 is still unclear (6). Further research is recommended to investigate and access probable correlations between COVID-19 and female reproduction and SARS-CoV-2 social, economic and health consequences on fertility.



**Figure 1.** The proposed mechanism of the COVID-19 vaccine for menstrual changes

### The menstrual changes after the COVID-19 vaccination

Vaccination is one of the best ways to eradicate COVID-19 and save people's lives (27). Despite this, many women are complaining of menstrual disturbances like postmenopausal bleeding, heavy menstrual bleeding and polymenorrhea after receiving

a second dose of the COVID-19 vaccine across the world (28). Also, some rumors and anecdotal reports, spread through social media, suggest that COVID-19 vaccines cause female sterility (29). COVID-19 vaccines have some approved side effects like fever, fatigue, headache, etc (30). But, according to recent research, there is no evidence showing that COVID-19

vaccines can influence menstruation (31, 32). and most of the women who reported changes in their menstrual cycle explained that the irregularities go back to normal in a subsequent cycle (32). After injection of either mRNA or adenovirus-vectored SARS-CoV-2 vaccines, menstruation irregularities have been reported. According to this information, there are hypotheses suggesting that if there is a link between menstrual changes and COVID-19 vaccines, it is probably related to the reaction of the immune system against vaccines, not a particular vaccine ingredient (32-35). It can play a role through immune cells that are part of the cyclical breakdown and buildup of the uterus and also immune system impacts on the hormones driving the menstrual cycle (32, 36-38). Also, until now, research and studies have shown that COVID-19 vaccines have no considerable influence on fertility (33, 39, 40) or follicular function (29).

At last, stating a definite opinion about the effects of vaccination on menstruation needs more large-scale studies with long-term follow-up to evaluate all aspects of it.

#### **Impact of the COVID-19 vaccine on female fertility and reproduction**

One of the main concerns of society about the COVID-19 vaccine, is its effects on women's fertility (41). Which could be due to some claims in social media suggesting the cross-reaction of antibodies against the virus spike protein resulting from the vaccine with syncytin-1 (42). Any damage to syncytin-1 which is an essential part of implantation, may lead to failed implantation, early pregnancy loss or some further problems regarding placentation (43). The previously mentioned cross-reaction seems unlikely, as a total identity of <7% between the virus spike protein and syncytin-1 was reported by UniProt alignment. Also, another antibody (GNbAC1, Temelimab; geneuro) that has been developed for the treatment of multiple sclerosis had no effects on the function of syncytin, despite the high similarity (overall homology of 81% (44) between its target and syncytin-1. It can reject the possibility of cross-reaction even more (45).

In vitro fertilization with frozen embryo transfer (FET), carried out by Morris, indicated that Pfizer and Moderna vaccines did not have any impacts on implantation rate, trophoblast development, and the results were similar in SARS-CoV-2 vaccine seropositive, infection seropositive and seronegative women (43).

An experimental study in female rats demonstrated that pre-coital interval, estrous cyclicity, mating, fertility or pregnancy indices are not affected by the BNT162b2 COVID-19 vaccine, since no changes were detected in the reproductive organs of non-pregnant female rats on a microscopic level. This study indicates intact fertility and reproduction, and there were only some non-adverse clinical signs due to the inflammatory response to the vaccine (46).

In the immediate subsequent IVF cycle of patients, the BNT162b2 vaccine had no remarkable effects on ovarian reserve, characteristics of ovarian stimulation, the developing gametes/embryos, the proportion of top-quality embryos, or embryological parameters. Moreover, the pregnancy rate was also acceptable, which might be due to the slight effect of the vaccine on folliculogenesis and spermatogenesis and a lower degree of systemic inflammation caused by it. Unlike COVID-19 active infection, any environmental inflammatory process following the COVID-19 vaccine, did not disturb the folliculogenesis process (47). Also, in patients treated in the IVF unit that were vaccinated with this mRNA vaccine for Intracytoplasmic sperm injection (ICSI) cycle outcome, parameters related to embryo and pregnancy rate had no significant changes in comparison to pre-vaccination (48) The mRNA COVID-19 vaccine in pregnant women has no effect on pregnancy or neonatal outcomes such as neonatal death, congenital anomalies, or preterm birth (49).

#### **Conclusion**

From 2019 until now, the COVID-19 pandemic has yielded many pathological outcomes involving systems like the gastrointestinal, neurologic and cardiovascular systems (50). There has been worldwide concern about the side effects of the COVID-19 vaccination, leading to a rejection of its administration. In this study, we investigated the side effects of COVID-19 and its vaccination on menstruation and the female reproductive system.

SARS-CoV-2 infection has been reported to temporarily cause shortened cycle length and increased menstrual bleeding (10). According to another study, the majority of women did not have any menstruation abnormalities, but some of them reported irregularities such as dysmenorrhea, amenorrhea, and oligomenorrhea (11). Therefore, it might cause ovarian and fertility dysfunction, but the extent of its effect on fertility remains unclear.

The COVID-19 vaccination has been reported to induce postmenopausal bleeding, heavy menstrual bleeding, and polymenorrhea. However, most of the patients went back to their routine in the following cycle, and it has been considered a result of an immune response. Moreover, the hypothesis of a cross-reaction between antibodies against the virus spike protein and syncytin-1 was denied by a low similarity in the alignment. There was no indication of unexpected safety signals regarding the effects of the COVID-19 vaccine on fertility. However, monitoring and disseminating information about this issue is still needed.

This study aims to lower women's concerns about the possible consequences of COVID-19 vaccine administration. Nevertheless, further research and experimental data are needed to provide more evidence

and evaluations regarding menstruation and female reproductivity.

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## Conflict of Interest

There are no conflicts of interest.

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