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Female reproduction and abnormal uterine bleeding after COVID-19 vaccination

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Coronavirus disease 2019 (COVID-19) vaccines have been widely administered throughout the global community to minimize the morbidity and mortality caused by the COVID-19 pandemic. Although generally well-tolerated, these vaccines have generated some unwanted consequences, including thrombosis and menstrual irregularities. The effect of vaccination on female reproductive function has also been questioned. The aim of this review is to give readers a clear understanding of the effects of COVID-19 vaccines on thrombosis, reproductive function, and menstrual irregularities by systemically analyzing the available literature. The available evidence suggests that COVID-19 vaccines have a minimal impact on ovarian reserve. Furthermore, *in vitro* fertilization outcomes after COVID-19 vaccination remain unimpaired compared to those who did not receive the vaccines. Current evidence supports a certain degree of impact of COVID-19 vaccines on the menstrual cycle, with the most frequent alteration being menstrual irregularity, followed by menorrhagia. These changes are generally well-tolerated and transient, lasting less than 2 months. This review, by providing information with up-to-date references on this issue, may enhance readers' understanding of the impact of COVID-19 vaccines on female reproductive function and the menstrual cycle.

Keywords: COVID-19; Fertilization *in vitro*; Menstruation; Menstruation disturbances; Vaccination

Introduction

Since its outbreak in 2019, the coronavirus disease 2019 (COVID-19) pandemic has swept through the globe with catastrophic consequences. According to the World Health Organization (WHO), as of December 23, 2022, there have been 660.75 million confirmed cases of COVID-19 and 6.69 million deaths worldwide [1]. The deleterious effects of COVID-19 have led to the development of vaccines to halt the disease's rapid spread worldwide and minimize its impact. COVID-19 vaccination began in December 2020, almost a year after the pandemic began. Several COVID-19 vaccines have been validated for use by the WHO. The most prominent makers of vaccines are Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Johnson & Johnson (J&J)/Janssen.

Consequently, the scientific community has expanded its scope of interest from the pandemic itself to the adverse effects of vaccines. There have been many investigations regarding the relationship between COVID-19 vaccination and female reproductive health. This research is critical, as it serves as a basis for altering the health-related behaviors of the general population, with potential impacts on overall health outcomes, and as evidence for many governmental policies.

The Korean Specialized Committee for the compensation of loss after COVID-19 vaccination has decided to include abnormal uterine bleeding (AUB) as a "suspected related symptom" after COVID-19 vaccination on August 16, 2021, for all vaccine types, including those manufactured by Oxford-AstraZeneca, Moderna, Pfizer-BioNTech, and J&J. This decision has enabled those who developed AUB after vaccination for COVID-19 to claim compensation from the committee and receive support. The scientific basis for this decision was the analysis by the COVID-19 Vaccine Safety Committee of the National Academy of Medicine of Korea. After a comprehensive analysis of

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domestic and international data on adverse reactions reported after COVID-19 vaccination, the committee has announced the discovery of a statistically significant association between AUB and COVID-19 vaccination, which is sufficient evidence to establish a causal relationship.

This article specifically focuses on the effect of COVID-19 vaccines on female reproductive health, including thrombosis, ovarian function, *in vitro* fertilization (IVF) outcomes, and the menstrual cycle.

COVID-19 vaccination and thrombosis

In 2021, Schultz et al. [2] reported five healthcare workers who experienced thrombosis after administration of the ChAdOx1 nCov-19 vaccine (AstraZeneca). In the same year, Scully et al. [3] reported thrombosis in 23 patients after receiving the same vaccine.

The adverse events of special interest after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine include deep vein thrombosis, disseminated intravascular coagulation, and pulmonary embolism. The reported thrombotic conditions mainly include venous thrombosis, with the most common location being cerebral venous sinus thrombosis and cerebral venous thrombosis. Other conditions include arterial thrombosis, organ thrombosis, infarction, thrombophlebitis, thrombotic microangiopathy, and transient ischemic attack [4].

1. Incidence

The reported incidence of thrombosis after vaccination is very low (0.00006% to 0.005%). No significant difference in incidence has been reported according to the type of vaccine [5-8]. However, inconsistencies exist in this regard; for instance, in another report, thrombotic events occurred most frequently with the Pfizer vaccine (55.4%) than with the Moderna (10.5%) and AstraZeneca (29.6%) vaccines [8]. In a systemic review by Al-Ali et al. [9], a higher incidence of thrombosis as a vaccine adverse event was noted for the AstraZeneca vaccine. That study analyzed 460 thrombotic events, and found that 9.8% were from the Pfizer-BioNTech vaccine, 81.5% from the AstraZeneca vaccine, and 8.7% from the J&J Janssen vaccine [9].

There is no apparent trend according to sex in the occurrence of thrombotic events after vaccination among studies; however, in a study by Tobaiqy et al. [7], more female patients than male patients experienced thrombotic events. In another meta-analysis investigating the relationship between COVID-19 vaccines and thrombosis, a combined analysis of the population that received the AstraZeneca vaccine showed a female preponderance compared to those who received other vaccines [10].

2. Mechanisms

One of the proposed mechanisms of thrombosis after vaccination is the formation of a complex between vaccine-induced antibodies and platelet factor 4, which may lead to a hypercoagulable state with platelet depletion. Other possible mechanisms include adenoviral vectors from vaccines acting as a possible aggregating agent with platelets, causing thrombosis [2,10].

COVID-19 vaccination and ovarian function

Concerns have been raised, albeit without scientific evidence, about the negative impact of COVID-19 vaccines on female fertility. The COVID-19 pandemic has changed the behaviors of the fertile population trying to conceive. However, there is a lack of scientific evidence proving the negative impact of the COVID-19 vaccine on pregnancy outcomes [11]. To date, there is no evidence that the COVID-19 vaccine affects female infertility. The American Society for Reproductive Medicine issued an updated a guidance document in December 2020 stating that individuals who are planning to conceive are not recommended to refrain from receiving COVID-19 vaccination [12].

1. Animal studies

An experiment using 44 female rats that were administered the BNT162b2 mRNA vaccine (Pfizer-BioNTech) was conducted to evaluate its safety regarding reproductive function and pregnancy. The vaccine showed no adverse effect on reproductive function, pregnancy, delivery, or the development of offspring. The pregnancy rate of rats in both groups was similar, with a 95% pregnancy rate in the vaccine group and a 98% rate in the control group [13]. Nonetheless, the nature of an animal study necessitated further research on the direct effect of COVID-19 vaccination on human ovarian function.

2. Human studies

Ovarian function in humans refers to the ability to produce a mature ovum to be fertilized with sperm for the production of offspring, as well as the ability to produce sex hormones. For the former definition, the term "ovarian reserve" is used to assess and predict the remaining ovarian function in women of reproductive-age. Anti-Müllerian hormone (AMH), a glycoprotein of the transforming growth factor-beta family produced by granulosa cells of the ovary, best serves the purpose of estimating the functional ovarian reserve, as noted by many researchers [14,15]. Another powerful tool for assessing the ovarian reserve is the antral follicle count (AFC), which, like AMH, is also closely correlated with age and declines with impending menopause [16,17].

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The AFC of the vaccinated and unvaccinated populations has been reported to be similar in most studies. In a small cohort study that investigated the effect of the Pfizer-BioNTech vaccine on reproductive function, the mean AFC of the vaccinated, COVID-19-positive, and control groups before the start of IVF were all similar [18]. Another study with a larger population showed that the AFC of the population vaccinated with either Pfizer or Moderna vaccines was comparable to that of the unvaccinated population, with no statistically significant difference [19]. For CoronaVac or Sinopharm, which are inactivated vaccines, the vaccinated group had an AFC of 14.5 while the unvaccinated group had an AFC of 16, which was a statistically significant difference [20]. However, that research was subject to limitations since it was a retrospective observational study of different groups, without adjustment for age or surgical history. Moreover, in the same study, the IVF outcomes, including the ovarian response and retrieved oocytes, were comparable after propensity score matching. In contrast to previous research that reported differences in the AFC, another study investigating the effects of inactivated vaccines demonstrated that the AFC was similar in the vaccinated and unvaccinated populations after propensity score matching [21]. Lastly, Requena et al. [22] evaluated the effects of various types of vaccines in comparison with unexposed groups. The AFC was comparable across populations vaccinated with different types of vaccines. The parameters of the same patients before and after vaccine administration were also compared, and the pre-vaccination and post-vaccination AFCs were consistently similar.

Three studies investigated differences in AMH levels between vaccinated and unvaccinated patients. Aharon et al. [19] observed no difference in AMH values between vaccinated (with either the Pfizer or Moderna vaccine) and unvaccinated populations (2.9 ± 2.9 vs. 2.7 ± 2.6, $p = 0.38$). A study by Wu et al. [20] also found no significant difference in AMH levels between vaccinated and unvaccinated populations. In this study, the AFC of the vaccinated group was slightly lower than that of the unvaccinated group, as previously mentioned. However, AMH levels, which constitute a more accurate measure of ovarian reserve, were similar, highlighting that vaccine administration was not associated with impaired ovarian reserve. Lastly, a more recent publication by the same group that investigated frozen embryo transfers reported comparable AMH levels between vaccinated and unvaccinated populations [23].

COVID-19 vaccination and IVF outcomes

1. Anti-SARS-CoV-2 immunoglobulin G level

Positive results were found for the serum anti-SARS-CoV-2 immunoglobulin G in those who had received vaccination or were infected with COVID-19, and the levels correlated with follicular fluid. Odeh-Natour et al. [24] analyzed the impact of the Pfizer-BioNTech vaccine on IVF treatment outcomes. Patients were classified based on their anti-spike (S) and anti-nucleotide (N) levels. After controlled ovarian hyperstimulation (COS), vaccinated, previously infected, and all-negative patients had similar numbers of follicles and mature oocytes, as well as comparable fertilization, cleavage, and pregnancy rates [24].

2. COS outcomes

Details of the previous studies are summarized in Table 1. Several studies have investigated the effect of the Pfizer and Moderna vaccines, and no statistically significant differences were observed in the oocyte number, mature oocyte number, fertilization rate, or blastocyst formation rate [19,22,25,26]. Likewise, no significant differences were found in follicle- stimulating hormone (FSH) or human menopausal gonadotropin (hMG) doses and the length of stimulation. For adenoviral vaccines such as Janssen and AstraZeneca, there were no significant differences in total doses of FSH or hMG, stimulation days, oocyte numbers, mature oocyte numbers, fertilization rates, or blastocyst formation rates [22]. For inactivated vaccines such as CoronaVac manufactured by Sinovac, no differences were observed in ovarian stimulation profiles and IVF outcomes [20,21,23].

Two studies used historical controls to compare IVF outcomes—in other words, the same population was studied before and after vaccination [22,25]. Both studies showed no differences in patients' IVF outcomes before and after vaccinations Vaccine administration did not increase the aneuploidy rate. A study investigating the effect of preimplantation genetic testing for aneuploidy in the vaccinated and unvaccinated populations found that the euploidy rate was similar between vaccinated and unvaccinated populations after multivariable linear regression and adjusted analysis [19].

3. Pregnancy outcomes

Studies with Pfizer, AstraZeneca, Janssen, Moderna, and Sinopharm vaccines have shown similar pregnancy rates between vaccinated and unvaccinated patients [19-21,24,27,28]. The implantation rates and miscarriage rates were also similar. The vaccine did not increase complication rates after IVF and embryo transfer. Two studies investigated the ectopic pregnancy rate, which was similar among the two groups [20,23]. A study found no significant difference in the incidence of ovarian hyperstimulation syndrome (OHSS) between vaccinated and unvaccinated groups [20].

Furthermore, the interval between vaccine administration and embryo transfer did not affect pregnancy outcomes. Pregnancy rates were similar when patients were classified based on their time from

Table 1. Studies investigating the effects of COVID-19 vaccines on IVF-ET

Study	Country	Study design	No. of patients	Vaccine type	Dosage, interval between vaccination and IVF-ET	No. of oocytes	No. of mature oocytes	Fertilization rate (%)	Blastulation rate (%)	Implantation rate (%)	Clinical pregnancy rate (%)	Miscarriage rate (%)
Aharon et al. (2022) [19]	USA	Retrospective cohort study	COS: Vaccinated (n = 222) Unvaccinated (n = 983) ET: Vaccinated (n = 214) Unvaccinated (n = 733)	Pfizer-BioNTech, Moderna	2 doses of vaccines 14 days before start of IVF	15.9 (14.4–17.5) vs. 15.0 (14.4–15.6) (NS) (vaccinated vs. unvaccinated)	12.2 (11.0–13.3) vs. 11.2 (10.7–11.7) (NS)	80.7 (78.4–83.0) vs. 78.7 (77.5–80.0) (NS)	62.9 (59.4–66.4) vs. 60.0 (58.2–61.7) (NS)	NA	59.5 (52.7–66.3) vs. 63.7 (60.2–67.3) (NS)	18.0 (11.1–24.9) vs. 12.0 (9.0–15.0) (NS)
Avraham et al. (2022) [26]	Israel	Retrospective cohort study	Vaccinated (n = 200) Unvaccinated (n = 200)	Pfizer-BioNTech	2 doses, at least 2 weeks before ovarian stimulation	8.47 (7.52–9.42) vs. 8.32 (7.38–9.27) (NS) (vaccinated vs. unvaccinated)		64.81 (60.6–68.93) vs. 61.98 (57.37–66.60)			32.8 vs. 33.1 (NS)	
Bentov et al. (2021) [18]	Israel	Prospective cohort study	Recovering from COVID-19 (n = 9) Vaccinated (n = 9) Uninfected and non-vaccinated (n = 14)	Pfizer-BioNTech	1–2 doses, mean 32.2 days (to oocyte retrieval day)	12.4 ± 8.7 vs. 10.89 ± 4.8 vs. 11.2 ± 6.7 (NS) (vaccine vs. COVID-19 vs. control)	7.25 ± 2.77 vs. 8.37 ± 4.1 vs. 7.75 ± 4.7 (NS)					
Brandao et al. (2022) [28]	Spain	Retrospective cohort study	Vaccinated (n = 890 ETs) Non-vaccinated (n = 3,272 ETs)	Pfizer-BioNTech, Moderna	1–2 doses, median 3.2 months (vaccination to ET)						70.4 vs. 70.6 (NS)	
Cao et al. (2022) [23]	China	Retrospective cohort study	Vaccinated (n = 502) Non-vaccinated (n = 1,589)	Inactivated vaccines (Sinopharm, Sinovac)	1–2 doses, median time interval 117.5 days (vaccination and FET)						54.7 vs. 54.2 (NS)	11.3 vs. 11.4 (NS)
Huang et al. (2022) [21]	China	Retrospective cohort study	Vaccinated (n = 146) Unvaccinated (n = 584)	Sinopharm or Sinovac	2 doses, mean time interval 72.4 days	9.9 ± 7.1 vs. 9.9 ± 6.7 (NS) (vaccinated vs. unvaccinated)	8.3 ± 6.1 vs. 7.9 ± 5.6 (NS)	71.1 ± 23.3 vs. 70.2 ± 23.9 (NS)	74.5 ± 30.5 vs. 71.6 ± 31.3 (NS)	45.4 vs. 46.7 (NS)	59.1 vs. 63.6 (NS)	NA
Odeh-Natour et al. (2022) [24]	Israel	Prospective cohort study	Vaccinated (n = 37) Unvaccinated (n = 22)	Pfizer-BioN-Tech	2 doses, 2–8 weeks after the second vaccination	10.05 ± 7.6 vs. 12.3 ± 9.11 vs. 11.89 ± 9.67 (NS) (positive anti-S/ positive anti-N/ negative anti S, N)	6.13 ± 4.66 vs. 4.66 ± 3.70 vs. 8.2 ± 6.5 (NS)	49/60/58 (NS)			44/33/50 (NS)	

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Table 1. Continued

Study	Country	Study design	No. of patients	Vaccine type	Dosage, interval between vaccination and IVF-ET	No. of oocytes	No. of mature oocytes	Fertilization rate (%)	Blastulation rate (%)	Implantation rate (%)	Clinical pregnancy rate (%)	Miscarriage rate (%)
Orvieto et al. (2021) [25]	Israel	Observational study	36 (historical control of same patients)	Pfizer-BioNTech	2 doses, 7–85 days from second vaccine to IVF treatment	9.7 ± 6.7 vs. 10.1 ± 8 (NS) (pre-vaccination vs. post-vaccination)	7.94 ± 5.7 vs. 8.0 ± 6.5 (NS)					
Requena et al. (2023) [22]	Spain	Retrospective observational Study	Vaccinated (n = 510) (Janssen n = 31, AstraZeneca n = 38, Pfizer-BioNTech n = 336, Moderna n = 105) Unexposed (n = 1,190)	Janssen, AstraZeneca, Pfizer-BioNTech, Moderna	2 doses, average of 2 months after the second dose	9.2/7.7/9.8/8.8/10.2 (NS) (AstraZeneca/Janssen/ Moderna/Pfizer/ Unvaccinated)	6.7/5.8/8.3/ 7.2/8.5 (NS)	80/78/70/81/75 (NS)	41.1/45.5/40.9/ 42.0/45.2 (NS)			
Wu et al. (2022) [20]	China	Retrospective cohort study	Vaccinated (n = 239) Unvaccinated n = 928 (after PSM)	Sinopharm CoronaVac	1–2 doses, median 31–60 days to ovarian stimulation	8 (5–12) vs. 9 (5–12) (NS) (vaccinated vs. unvaccinated)	NA	80.0 vs. 79.7 (NS)	48.9 vs. 49.3 (NS)	35.4 vs. 38.3 (NS)	44.4 vs. 47.4 (NS)	15.0 vs. 12.1 (NS)
Zhao et al. (2023) [27]	China	Retrospective cohort study	Vaccinated (n = 781) Unvaccinated (n = 1,851)	Inactivated vaccines	Varies (≤ 3 or > 3 months)						47.5 vs. 47.7 (NS)	Clinical pregnancy loss rate: 12.6 vs. 11.8 (NS)

COVID-19, coronavirus disease 2019; IVF, *in vitro* fertilization; ET, embryo transfer; COS, controlled ovarian hyperstimulation; NS, not significant; NA, not available; PSM, propensity score matching.

vaccination to embryo transfer into four quartiles, with a median of 3.2 months [28]. A recent study by Zhao et al. [27] compared pregnancy rates among patients classified based on the time interval between vaccination completion and embryo transfer. Individuals vaccinated with time intervals of less than 3 months and more than 3 months had similar clinical pregnancy and clinical pregnancy loss rates [27].

In summary, the IVF outcomes after vaccination with mRNA vaccines (Pfizer and Moderna), adenoviral vaccines (Janssen and AstraZeneca), or inactivated vaccines (Sinopharm) are comparable with those of unvaccinated individuals. The pre- and post-vaccination IVF outcomes are also similar. According to currently available data, rates of euploidy, OHSS, and ectopic pregnancy all seem comparable between vaccinated and unvaccinated populations. The time interval between vaccine administration and embryo transfer does not seem to interfere with pregnancy outcomes.

COVID-19 vaccination and the menstrual cycle

1. Incidence

The incidence of menstruation-related changes after COVID-19 vaccination varies significantly among published studies. A retrospective study in Saudi Arabia investigated patients who received either the Pfizer or AstraZeneca vaccine. An abnormal menstrual cycle was reported by 0.69% of those vaccinated with the Pfizer vaccine and 0.45% of those who received the AstraZeneca vaccine [29]. In an African study where individuals were vaccinated with mostly AstraZeneca (77.8%, followed by Pfizer [9.1%]), menstrual disorders were reported in 0.5% of patients [30]. A Chinese study that investigated the side effects of healthcare workers after administration of the inactivated vaccine (Sinopharm) showed menstrual changes in 2.1% [31]. The most frequent type of menstrual change was menstrual delay, followed by early menstruation. In some reports, the percentage tended to be higher when the reproductive-age population was targeted. One study showed that when the population was narrowed down to menstruating, reproductive-age women, 4.8% of patients reported menstruation-related symptoms [32].

2. Mechanisms

A proposed mechanism for COVID-19 vaccination-induced alterations in the menstrual cycle is that vaccination may function as a potential stressor to the human body, disrupting the hypothalamic-pituitary-ovarian axis [33]. Furthermore, immunological or inflammatory reactions following vaccine administration may play a role, interfering with menstrual homeostasis and creating hormonal disruptions [34]. Heavy menstrual bleeding may be due to the increased bleeding tendency after COVID-19 vaccination [35]. The specific mechanisms underlying the clinical symptoms may need further investigation and validation.

3. Menstrual irregularities

Studies have reported a higher incidence of menstrual irregularities after COVID-19 vaccination. A prospective cohort study by Edelman et al. [36] recruited volunteers to investigate the effects of COVID-19 vaccines on menstrual symptoms (n = 545) and found that 25% of patients reported changes in their menstrual cycle. Another similar study reported that about 50% to 60% of women of reproductive-age had menstrual irregularities [34]. An Israel survey-based study that enrolled only pre-menopausal non-pregnant patients (n = 7,904) reported that 47.2% of patients had changes in menstrual patterns [35]. These discrepancies in the incidence of menstrual side effects after the vaccine may be because larger population-based studies include all female patients regardless of their menstrual status or reproductive function, and specific information on incidence in tailored populations is unavailable. The short duration of surveillance, up to about a week in a larger population study, may have also had an impact. Additionally, there is a selection bias for recruiting those who participate in questionnaires related to menstrual irregularities; reproductive-age women with a keen interest in their menstrual patterns are more likely to be included in the questionnaire cohort.

COVID-19 vaccines influence the interval between cycles, the duration of the cycle, and the severity of symptoms, including menorrhagia and dysmenorrhea. Among various features presented as menstruation-related side effects of COVID-19 vaccines, the most commonly reported symptom is menstrual irregularity. In a study by Wong et al. [37] that analyzed 5,975,363 text responses entered into the V-safe surveillance application administered by the government, 1% (n = 62,679) reported menstrual irregularities or vaginal bleeding as a complication after COVID-19 vaccination. The most common theme was the timing of menstruation (83.6%), followed by menstrual symptom severity (67.0%). The reported symptoms were mainly within 0 to 7 days after vaccination [37]. In another study by Farland et al. [38], 25% of 545 individuals reported menstrual cycle changes after vaccination, and the most common change was irregular menstruation (43%). Rodriguez Quejada et al. [39] reported that among 184 patients with menstrual alterations after vaccination of various types, 42.9% had menstrual irregularities.

Regarding the quantification of menstrual cycle irregularities, Edelman et al. [36] reported that the change was less than a day. In a prospective cohort study including 3,959 patients, the authors showed that the cycle length increased by 0.71 days after the first dose and 0.91 days after the second dose, with statistical significance. There was no significant change in the duration of menstruation [36]. In a survey study of 164 women by Lagana et al. [34], the

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participants reported varying frequencies and duration of menstruation. After the first dose of the COVID-19 vaccine, 18% to 33.3% of women reported menstruation 1 to 5 days earlier than expected. Regarding the length of menstruation, 16% to 67% of women reported that menstruation lasted for more than 7 days, while 11% to 37% reported that it lasted for less than 3 days. After the second dose, the trend of the answers was similar; although variation existed, the participants tended to have earlier (12% to 38%), longer (21% to 50%), and heavier (28% to 62%) menstruation [34].

4. Menstrual severity

Menorrhagia has also been commonly reported after COVID-19 vaccination. An Israeli survey of 7,904 pre-menopausal non-pregnant women by Issakov et al. [35] reported that 80.6% of those who reported menstrual alterations had menorrhagia, the most common menstrual problem encountered by the COVID-19 vaccinated population. In a study by Wong et al. [37], menstrual severity, or heavy bleeding, was the second most commonly reported event (67.0%). Another retrospective study reported heavy menstrual bleeding among 41.8% of 184 patients with menstrual alterations [39]. Other reported problems include a higher frequency of premenstrual symptoms in 34% of the population and increased dysmenorrhea in 30%. Amenorrhea was less common but reported in 3% to 11% of the population [39].

5. First dose vs. second dose

Conflicting results have been reported on whether menstruation-related side effects are more severe with the first or second dose. Farland et al. [38] and Lagana et al. [34] reported a higher frequency of menstruation-related side effects after the second dose. In the former study, 56% of participants reported alterations after the second dose and 18% after the first dose. In the latter study, 60% to 70% of women reported menstrual irregularities after the second dose, whereas only 50% to 60% reported menstrual irregularities after the first dose. However, Muhaidat et al. [40] reported more frequent symptoms after the first dose, with 46.7% reporting symptoms after the first dose and 32.4% after the second dose. The type of vaccine seems unrelated, as studies comparing menstruation-related symptoms in populations with different vaccines did not show inter-group differences [34,39].

Interestingly, according to a cross-sectional survey by Muhaidat et al. [40], menstrual alterations after the COVID-19 vaccine did not seem to be affected by underlying diseases such as polycystic ovarian syndrome, thyroid disease, myomas, endometriosis, and adenomyosis. Several studies have shown that menstrual changes are only transient, usually resolving within 2 months [34,40].

Conclusion

Although COVID-19 vaccines have been proven to be generally safe, they may produce unwanted consequences. The main findings of this review are as follows:

Although rare, thrombosis may occur after vaccine administration (incidence, 0.00006% to 0.005%).

The impact of COVID-19 vaccines on ovarian reserve (AMH and AFC) is minimal.

IVF outcomes are not impaired after COVID-19 vaccine administration.

COVID-19 vaccines certainly seem to affect the menstrual cycle; however, the effects are generally well-tolerated and transient. The most frequently reported problems are menstrual irregularities, followed by menorrhagia. However, the findings of recent studies are generally reassuring, as symptoms resolve within about 2 months.

It remains unclear whether certain groups are particularly vulnerable to menstruation-related adverse events following COVID-19 vaccination. The natural pregnancy rates following vaccination also remain unclear. Further investigations may help the scientific community understand the remaining questions regarding the effects of COVID-19 vaccines on female reproductive function and menstruation.

Conflict of interest

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

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Author contributions

Conceptualization: SKK. Data curation: HP. Formal analysis: HP, SKK. Methodology: HP, SKK. Project administration: SKK. Writing-original draft: HP. Writing-review & editing: HP, SKK.

References

1. World Health Organization. WHO coronavirus (COVID-19) dashboard [Internet]. WHO; 2023 [cited 2023 May 3]. Available from: https://covid19.who.int/
2. Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen

F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124–30.
3. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2202–11.
4. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology. CBER Surveillance Program: background rates of adverse events of special interest for COVID-19 vaccine safety monitoring protocol 2021 [Internet]. FDA; 2021 [cited 2023 May 3]. Available from: https://bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-FINAL-2020.pdf
5. Pawlowski C, Rincon-Hekking J, Awasthi S, Pandey V, Lenehan P, Venkatakrishnan AJ, et al. Cerebral venous sinus thrombosis is not significantly linked to COVID-19 vaccines or non-COVID vaccines in a large multi-state health system. J Stroke Cerebrovasc Dis 2021;30:105923.
6. Pottegard A, Lund LC, Karlstad O, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114.
7. Tobaiqy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 AstraZeneca vaccine reported to EudraVigilance database. Vaccines (Basel) 2021;9:393.
8. Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. Eur Respir J 2021;58:2100956.
9. Al-Ali D, Elshafeey A, Mushannen M, Kawas H, Shafiq A, Mhaimeed N, et al. Cardiovascular and haematological events post COVID-19 vaccination: a systematic review. J Cell Mol Med 2022;26:636–53.
10. Bilotta C, Perrone G, Adelfio V, Spatola GF, Uzzo ML, Argo A, et al. COVID-19 vaccine-related thrombosis: a systematic review and exploratory analysis. Front Immunol 2021;12:729251.
11. Flynn AC, Kavanagh K, Smith AD, Poston L, White SL. The impact of the COVID-19 pandemic on pregnancy planning behaviors. Womens Health Rep (New Rochelle) 2021;2:71–7.
12. American Society for Reproductive Medicine. Patient management and clinical recommendations during the coronavirus (COVID-19) pandemic [Internet]. ASRM; 2020 [cited 2023 May 3]. Available from: https://www.asrm.org/ globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate11.pdf
13. Bowman CJ, Bouressam M, Campion SN, Cappon GD, Catlin NR, Cutler MW, et al. Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine. Reprod Toxicol 2021;103:28–35.
14. Moolhuijsen LM, Visser JA. Anti-Mullerian hormone and ovarian reserve: update on assessing ovarian function. J Clin Endocrinol Metab 2020;105:3361–73.
15. Cedars MI. Evaluation of female fertility-AMH and ovarian reserve testing. J Clin Endocrinol Metab 2022;107:1510–9.
16. van Rooij IA, Broekmans FJ, Scheffer GJ, Looman CW, Habbema JD, de Jong FH, et al. Serum antiMullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. Fertil Steril 2005;83:979–87.
17. Bentzen JG, Forman JL, Larsen EC, Pinborg A, Johannsen TH, Schmidt L, et al. Maternal menopause as a predictor of anti-Mullerian hormone level and antral follicle count in daughters during reproductive age. Hum Reprod 2013;28:247–55.
18. Bentov Y, Beharier O, Moav-Zafrir A, Kabessa M, Godin M, Greenfield CS, et al. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. Hum Reprod 2021;36:2506–13.
19. Aharon D, Lederman M, Ghofranian A, Hernandez-Nieto C, Canon C, Hanley W, et al. In vitro fertilization and early pregnancy outcomes after coronavirus disease 2019 (COVID-19) vaccination. Obstet Gynecol 2022;139:490–7.
20. Wu Y, Cao M, Lin Y, Xu Z, Liang Z, Huang Q, et al. Inactivated COVID-19 vaccination does not affect in vitro fertilization outcomes in women. Hum Reprod 2022;37:2054–62.
21. Huang J, Xia L, Lin J, Liu B, Zhao Y, Xin C, et al. No effect of inactivated SARS-CoV-2 vaccination on in vitro fertilization outcomes: a propensity score-matched study. J Inflamm Res 2022;15:839–49.
22. Requena A, Vergara V, Gonzalez-Ravina C, Ruiz ME, Cruz M. The type of SARS-CoV-2 vaccine does not affect ovarian function in assisted reproduction cycle. Fertil Steril 2023;119:618–23.
23. Cao M, Wu Y, Lin Y, Xu Z, Liang Z, Huang Q, et al. Inactivated Covid-19 vaccine did not undermine live birth and neonatal outcomes of women with frozen-thawed embryo transfer. Hum Reprod 2022;37:2942–51.
24. Odeh-Natour R, Shapira M, Estrada D, Freimann S, Tal Y, Atzmon Y, et al. Does mRNA SARS-CoV-2 vaccine in the follicular fluid impact follicle and oocyte performance in IVF treatments? Am J Reprod Immunol 2022;87:e13530.
25. Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reprod Biol Endocrinol 2021;19:69.
26. Avraham S, Kedem A, Zur H, Youngster M, Yaakov O, Yerushalmi GM, et al. Coronavirus disease 2019 vaccination and infertility treatment outcomes. Fertil Steril 2022;117:1291–9.
27. Zhao Y, Zhao Y, Ai A, Jin L. Association of inactivated COVID-19

vaccination with in vitro fertilization and early pregnancy outcomes. J Med Virol 2023;95:e28432.
28. Brandao P, Pellicer A, Meseguer M, Remohi J, Garrido N, Garcia-Velasco JA. COVID-19 mRNA vaccines have no effect on endometrial receptivity after euploid embryo transfer. Reprod Biomed Online 2022;45:688–95.
29. Alghamdi AN, Alotaibi MI, Alqahtani AS, Al Aboud D, Abdel-Moneim AS. BNT162b2 and ChAdOx1 SARS-CoV-2 post-vaccination side-effects among Saudi vaccinees. Front Med (Lausanne) 2021;8:760047.
30. Anjorin AA, Odetokun IA, Nyandwi JB, Elnadi H, Awiagah KS, Eyedo J, et al. Public health surveillance for adverse events following COVID-19 vaccination in Africa. Vaccines (Basel) 2022;10:546.
31. Cheng Y, Li T, Zheng Y, Xu B, Bi Y, Hu Y, et al. Self-reported adverse events among Chinese healthcare workers immunized with COVID-19 vaccines composed of inactivated SARS-CoV-2. Hum Vaccin Immunother 2022;18:2064134.
32. Dar-Odeh N, Abu-Hammad O, Qasem F, Jambi S, Alhodhodi A, Othman A, et al. Long-term adverse events of three COVID-19 vaccines as reported by vaccinated physicians and dentists, a study from Jordan and Saudi Arabia. Hum Vaccin Immunother 2022;18:2039017.
33. Girardi G, Bremer AA. Scientific evidence supporting coronavirus disease 2019 (COVID-19) vaccine efficacy and safety in people planning to conceive or who are pregnant or lactating. Obstet Gynecol 2022;139:3–8.
34. Lagana AS, Veronesi G, Ghezzi F, Ferrario MM, Cromi A, Bizzarri M, et al. Evaluation of menstrual irregularities after COVID-19 vaccination: results of the MECOVAC survey. Open Med (Wars) 2022;17:475–84.
35. Issakov G, Tzur Y, Friedman T, Tzur T. Abnormal uterine bleeding among COVID-19 vaccinated and recovered women: a national survey. Reprod Sci 2023;30:713–21.
36. Edelman A, Boniface ER, Male V, Cameron ST, Benhar E, Han L, et al. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. BMJ Med 2022;1:e000297.
37. Wong KK, Heilig CM, Hause A, Myers TR, Olson CK, Gee J, et al. Menstrual irregularities and vaginal bleeding after COVID-19 vaccination reported to v-safe active surveillance, USA in December, 2020-January, 2022: an observational cohort study. Lancet Digit Health 2022;4:e667–75.
38. Farland LV, Khan SM, Shilen A, Heslin KM, Ishimwe P, Allen AM, et al. COVID-19 vaccination and changes in the menstrual cycle among vaccinated persons. Fertil Steril 2023;119:392–400.
39. Rodriguez Quejada L, Toro Wills MF, Martinez-Avila MC, Patino-Aldana AF. Menstrual cycle disturbances after COVID-19 vaccination. Womens Health (Lond) 2022;18:17455057221109375.
40. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual symptoms after COVID-19 vaccine: a cross-sectional investigation in the MENA region. Int J Womens Health 2022;14:395–404.