Transient Changes to the Menstrual Period in Women from Argentina Following Covid-19 Vaccination

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ABSTRACT

Several vaccines against SARS-CoV-2 were developed in the last year and worldwide used to prevent further viral spreading. The main side effects caused by these vaccines include anaphylactic shock, pain at the administration site, fever, fatigue, myalgia, headache, and nausea. Although not listed as a side effect, period disturbance and vaginal bleeding have been reported repeatedly by women shortly after vaccination. We surveyed menstruating women who received at least one dose of any vaccine against SARS-CoV-2 used in Argentina during August 1 to September 8, 2021. Overall, 40% of the women who participated in the survey reported an alteration of their period. Disturbance in the menstrual period was more frequent in younger women. Menstrual cycle disturbances were manifested both with mRNA, viral vector, and inactivated virus-vaccines.

Keywords: SARS-CoV-2, COVID-19, vaccine, menstrual cycle.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome-2

COVID-19: Coronavirus disease 2019

SAPREF: Argentine Society for the Preservation of Fertility

DOMB: delayed onset of menstrual bleeding

SOMB: skip onset of menstrual bleeding

INTRODUCTION

On December 31, 2019, the World Health Organization was first alerted to a cluster of pneumonia cases of unknown etiology in the city of Wuhan (Hubei, China). Subsequently, the International Committee on Taxonomy of Viruses (ICTV) designated the virus as Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) and the disease caused by it as Coronavirus Disease 2019 (COVID-19). From that date, several scientific investigations were carried out in relation to the etiology, pathogenesis, diagnosis, therapeutics, vaccines, among others, with the aim of knowing more about the disease and being able to treat and control it [1].
Currently, many drugs are under clinical trials or empirically included in treatment protocols for COVID-19. One of them is ivermectin (an antiparasitic drug), a previously Food and Drug Administration (FDA)-approved drug [2]. A clinical trial by Showman, et al. [3] suggest that ivermectin is an effective chemoprophylactic drug against COVID-19. On the other hand, the production of safe and effective vaccines to prevent further viral spread and recurrence in the world population has been one of the highest priorities. Currently, different vaccines, across four platforms, have been developed and worldwide used: mRNA vaccines [BNT162b2 (BioNTech / Pfizer); mRNA-1273 (Moderna)], non-replicative viral vector vaccines [Janssen (Janssen Pharmaceutical Company of Johnson & Johnson), ChAdOx1 nCoV-19 vaccine AZD1222 (AstraZeneca), Gam-COVID-Vac (Sputnik V), ChAdOx1 nCoV-19 Corona Virus Vaccine (Covishield), Ad5-nCoV (CanSino Biologics Inc)], and virus-inactivated vaccines [(inactive SARS COV-2 Vero cells (Sinopharm), CoronaVac (Sinovac, China)). The main side effects caused by these vaccines are anaphylactic shock, pain at the application site, fever, fatigue, myalgia, headache and nausea [4]. Although not listed as a side effect, period disturbance and vaginal bleeding have been reported repeatedly by women shortly after vaccination. Despite this, no alteration in fertility was yet reported. Seropositivity to the SARS-CoV-2 spike protein does not alter embryo implantation or early pregnancy development, whether acquired from infection or vaccination [5]. Although SARS-CoV-2 vaccination does not cause sterility, recent work by Victoria Male, et al. [6] revealed that more than 30,000 women reported suspected disturbances in menstrual periods or unexpected vaginal bleeding after vaccination at the Coronavirus Yellow Card Reporting Site in the United Kingdom. The University of Granada, Spain, recently started the EVA Project aimed to detect possible effects of vaccination against SARS-CoV-2 on the menstrual cycle of women of childbearing age. Unfortunately, the results of more than 80,000 women surveyed are not still published. In this context, the Argentine Society for the Preservation of Fertility (SAPREF) performed a survey to elucidate whether a possible correlation between SARS-CoV-2 vaccination and menstrual cycle disturbance exists.

MATERIALS AND METHODS

A voluntary, anonymous, and closed survey was conducted from August 1 to September 8, 2021, on menstruating women (18 to 40 years old) who reside in Argentina and received at least one dose of the SARS-CoV-2 vaccines currently administered in the country: AstraZeneca/AZD1222, inactive SARS COV-2 Vero cells (Sinopharm) or Gam-COVID-Vac (Sputnik V). The questionnaire mailed to participants included information on the number of doses received, vaccine received, menstrual cycle disturbance, type of disturbance [delayed onset of menstrual bleeding (DOMB) or skip onset of menstrual bleeding (SOMB)], days of early onset of the period, and the use of contraceptive methods. The exclusion criteria were: menstruating women under hormonal contraceptive methods, lactating women, irregular periods (regular menstrual cycle between 21 to 35 days), and pathologies involving menstrual cycle disturbances (e.g., polycystic disease, endometriosis, hypothyroidism, hyperthyroidism, hyperprolactinemia). The survey was reviewed and approved by the Institutional Ethics Committee from Universidad Maimónides. All participants consented to fill the survey anonymously.

RESULTS

From a total of 1,926 menstruating women answering the survey, 1,729 met the inclusion criteria. Three different age groups were established; Group 1, 18 to 25 years old (n=295); Group 2, 26 to 35 years old (n=1,037); Group 3, 36 to 40 years old (n=397).

The SARS-CoV-2 vaccine platform and the number of doses administered per age group are shown in Figure 1. The three vaccines used in Argentina at the time of this survey are represented in the three age groups at variable percentages according to their availability (Figure 1A). As expected following the strategy of vaccination established by the National Public Health Authority, the older the age group, the higher the percentage of 2 doses administered (Figure 1B).
Considering the total of women who answered the questionnaire, 40% declared having had some disturbance of her period after receiving the first dose (45%) or second vaccine dose (36%). Disturbance in the menstrual period was more frequent in younger women (Age group 1) regardless of having 1 or 2 vaccine doses (Figure 2). In this group, 51.19% reported a disturbance with the first dose and 38.33% with the second dose (Figure 3A) having a delayed or early onset of the period ranging from 1 to 7 days. The most frequent disturbance was DOMB in the appearance of menstrual bleeding (32.54%, first dose; 30%, second dose) (Figure 3A). It is important to point out that group 1 showed DOMB greater than 15 days with the second dose of the vaccine. In group 2, the main reported menstrual cycle disturbance was the DOMB in the appearance of menstrual bleeding regardless of the number of doses (first dose: 25.55% DOMB; second dose: 20.89% DOMB) (Figure 3A). Finally, group 3 showed 23.43% DOMB and 19.14% SOMB with the first dose and 17.80% DOMB and 18.85% SOMB with the second dose (Figure 3A). In both groups 2 and 3 the disturbance was observed mostly between 1-7 days (Figure 3B).
It is also important to mention that 64.1% of the participant women use an application to control their menstrual cycle and the contraceptive methods used were coito interruptus, condom, Copper Intrauterine Device (IUD), tubal ligation, vasectomy, and Billings ovulation method.

**DISCUSSION**

In the last time, women began to report disturbances in their menstrual cycle after receiving the SARS-CoV-2 vaccine. The frequency of period disturbance reports revealed the need for investigating the issue. In this way, the US National Institutes of Health allocated $1.67M for more in-depth research on the subject. In Argentina, the SARS-CoV-2 vaccination campaign began on December 29, 2020, and was carried out in stages, starting with essential workers, older adults and people with risk pathologies. Then, the vaccination campaign continued with the general population in decreasing age groups. This vaccination scheme is reflected in our study since most representative groups were 2 and 3, being younger women from group 1 the one with the smallest sample size. On the other hand, and according to the availability of vaccines that Argentina received at the time the survey was conducted, the Sinopharm vaccine was the most widely administered, followed by AstraZeneca and Sputnik V.

This is the first survey in Argentina that shows a correlation between disturbances in the menstrual cycle and the SARS-CoV-2 vaccine. In the youngest age group, the most frequent disturbance reported was the DOMB in the appearance of menstrual bleeding, being between 1 to 7 days with the first dose and more than 15 days with the second dose of the vaccine. The latter may be due to the administration of the Sinopharm vaccine, which has a 21 to 28 days interval between the first and second dose overlapping with the next menstrual cycle. In group 2, the most frequent disturbance was a DOMB in the menstrual cycle between 1 to 7 days, while in group 3 no differences were observed between the percentages of DOMB and SOMB. It is important to note that the main limitation of the study was an imperfect response rate resulting in a possible selection bias that may have affected the results. For example, there is a considerable risk of recall bias (perceived vs. actual menstrual disturbance) and participation bias (women with menstrual disturbance are more likely to respond to the questionnaire). Besides this, we believe mention the possible alteration of the menstrual cycle as a side effect should be considered.

Our results are in agreement with the observation of the Medicines and Healthcare Products Regulatory Agency from the United Kingdom (MHRA-UK) [7], indicating that the menstrual cycle disturbances are manifested both with mRNA, viral vector, and inactivated virus vaccines. The disturbance of the menstrual cycle may be due to an immune response rather than to specific components of the vaccine.

![Figure 3. (A) Disturbance in the menstrual cycle and (B) type and period of disturbance per group.](https://doi.org/10.30654/MJGO.10019)
Recent studies conducted with the HPV vaccine showed that one of the side effects after vaccination was irregular menstrual cycles and abnormal menstrual bleeding [8]. However, this study reported no correlation between the vaccine and the menstrual cycle disturbances, but with an immune response to the viral infection.

It is important to point out that fertility in women could be not affected by the SARS-CoV-2 infection or vaccines. Both oocyte quality and pregnancy rates were similar in vaccinated and unvaccinated women, and in vaccinated vs. sick women [5,9]. Moreover, Bentov, et al. [10] showed that neither the COVID-19 disease nor the SARS-CoV-2 vaccine caused a measurable detrimental effect on the function of the ovarian follicle. However, a recent publication by Herrero, et al. [11] suggests that infection with SARS-CoV-2 could damage ovarian function, alter the follicular microenvironment and potentially affect reproductive outcomes. Anyway, and according to our results, 4 out of 10 menstruating women in Argentina showed disturbances in the menstrual cycle following vaccination against SARS-CoV-2. Given the frequency of menstrual period disturbance, it should be listed as a possible side effect of SARS-CoV-2 vaccination.

Our observation showed that alterations in the menstrual cycle due to SARS-CoV-2 vaccines have a short-term duration and this is in agreement with a recent work by Edelman, et al. [12] that included unvaccinated versus vaccinated individuals and vaccination is associated with a small change in cycle length. On the other hand, the information currently available is controversial as to whether or not it affects fertility.

CONCLUSIONS

For all the above exposed, we consider that women should be informed of this as one of the possible side effects. Likewise, more research needs to be done on Sars-Cov-2 vaccines and their impact on the menstrual cycle and fertility to avoid misinformation, establish an appropriate plan of vaccination, and enable pregnancy planning.

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