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Review Article

Menstrual Irregularities Following Covid-19 Vaccinations

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Abstract:

Since 31 December 2019, when the WHO was informed of cases of pneumonia of unknown cause in Wuhan City, China; a novel coronavirus identified as the cause, has spread worldwide.

With an urgent need to slow viral transmission, decrease disease severity, and reduce mortality, biopharmaceutical companies rapidly began investigating potential COVID-19 vaccinations.

The American pharmaceutical company, Pfizer, in collaboration with the German company, BioNTech, developed a nucleoside-modified messenger RNA (modRNA) vaccine (BNT162b2), which was the first to receive an FDA permit for emergency use, with others following suit. Vaccine manufacturers provide a list of post-vaccination side effects with their preparations. Adverse vaccine reactions are evidence of the effectiveness of the vaccine and of increasing immunity against this disease. Interestingly, a growing number of women have reported menstrual irregularities after receiving COVID-19 vaccines. Those have been noted in post-authorization and post-licensure monitoring.

This review provides evidence that women experience menstrual abnormalities, including menorrhagia, metrorrhagia, and polymenorrhea following COVID-19 vaccines. The importance of the issue has been recognized by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency which decided to list heavy menstrual bleeding as a side effect as a side effect of unknown frequency in the product information for the SARS-CoV-2 mRNA vaccines.

Keywords: vaccinations; COVID-19; menstruation irregularities

Introduction

On 31 December 2019, the WHO was informed of cases of pneumonia of unknown cause in Wuhan City, China. A novel coronavirus was identified as the cause by Chinese authorities on 7 January 2020 and was temporarily named "2019-nCoV" [1]. Since then, it has spread worldwide.

With an urgent need to slow viral transmission, decrease disease severity, and diminish mortality, biopharmaceutical companies began investigating potential COVID-19 vaccinations [2].

The development of a novel vaccine is a labour intense and time-consuming process [2]. Prior to approval, a vaccine must first be theorized and tested in a laboratory environment. The resulting product can then be evaluated in Phase I clinical trials, which are focused on efficacy and conducted with a minimal number of participants (usually 20–100 healthy volunteers) [2]. Phase II clinical trials are designed to determine efficacy and safety, and several hundred volunteers may be included. In Phase III, incorporating thousands of participants, researchers confirm how well the vaccine works, monitor common and less common side effects [2]. Additionally, there is also Phase IV (after the approval), which is a formal, ongoing study to evaluate the new vaccine's safety and effectiveness over a longer period [3].

Despite the need for speed, safety and efficacy cannot be compromised and the FDA and other agencies have outlined guidance to address these areas of clinical development [3]. The preference would be a vaccine with longevity of protection, therefore required to receive an initial single dose or series, unlike other vaccinations that need an annual booster injection. An ideal candidate would also be easy to administer, such as orally or as an intramuscular injection, and stable under normal storage conditions. Additionally, in the setting of a pandemic, an ideal vaccine must be able to be rapidly manufactured and distributed. Finally, an ideal vaccine would retain activity against variants that may emerge or be easily modified to protect against them [2].

Despite the pressures, the researchers persevered and as part of the global race for a vaccine, the American pharmaceutical company, Pfizer, in collaboration with the German company, BioNTech, developed a

nucleoside-modified messenger RNA (modRNA) vaccine (BNT162b2), which was the first to receive an FDA permit for emergency use [4,5].

Following suit came other, that were registered in at least one country: mRNA vaccines (mRNA-1273-Moderna, CVnCoV-CureVac), viral vector vaccines (AZD1222- AstraZeneca/University of Oxford, Sputnik V-Gamaleya Research Institute, Sputnik V Light, Ad5-nCoV (Convidecia)-CanSino, Ad26.COV2.S- Johnson & Johnson), inactivated vaccines (NVX-COV2373- Novavax, CoronaVac-Sinovac Biotech, BBIBP-CorV-Sinopharm/Beijing Institute of Biological Product, Wuhan Sinopharm inactivated vaccine- Sinopharm/Chinese Academy of Science, Covaxin-Bharat Biotech, QazVac- Kazakh Research Institute for Biological Safety Problems, KoviVac- Chumakov Center, COVIran Barekat), and protein-based vaccines (EpiVacCorona-VECTOR, ZF2001- Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical, Abdala- Center for Genetic Engineering and Biotechnology (CIGB))[6].

Messenger RNA (mRNA) vaccines

BNT162b2, BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2 were the first authorized, mRNA-based vaccines. They contain the mRNA of the antigen of interest which enters cells and is translated into the spike protein to induce an immune response [6]. Briefly, mRNA vaccines inject cells with instructions to generate a protein that is normally found on the surface of SARS-CoV-2, the virus that causes COVID-19. By injecting cells with a synthetic mRNA that encodes a viral spike protein, an mRNA vaccine can direct human cells to make a viral spike protein and evoke an immune response without a person ever having been exposed to the viral material. These viral spike proteins, or antigens, normally coat the surface of the virus and are recognized by antibodies and other immune cells that prepare and protect the body against the virus. If a person is later exposed to the virus, antibodies and other parts of the immune system can recognize and attack the virus before it can infect healthy cells or cause illness [7].

Viral vector vaccines

Viral vectors are delivery systems containing nucleic acid encoding an antigen [8]. Viral vectors offer several advantages over traditional subunit vaccines, one of those being that in addition to eliciting potent antibody responses, they also elicit cellular responses that are crucial for the elimination of pathogen-infected cells. Additionally, viral vectors can induce high immunogenicity without the use of an adjuvant, as well as long-lasting immune responses. Additionally, viral vectors can be engineered to deliver vaccine antigens to specific cells or tissues [8].

Inactivated and protein subunit vaccines

Inactivated vaccines are whole viruses that cannot infect cells and replicate [9]. Subunit vaccines are made of fragments of proteins or polysaccharides. Protein-based vaccines allow one to make a protective response against a protein on the surface of a virus, against a protein on the surface of a bacteria, or against a secreted toxin. Hence, the immune response is against the protein components of the bacteria or virus, not the sugar coat. Certain proteins on the surface of bacteria or viruses help the pathogen cause disease, so inducing an immune response against them can help the body fight against the infection or the toxic effects of the toxin. Subunit vaccines can be made one of two ways: from the original pathogen or recombinantly. Recombinant vaccines use another organism to make the vaccine antigen [10].

Side effects of COVID-19 vaccinations

Vaccine manufacturers provide a list of post-vaccination side effects with their preparations. Adverse vaccine reactions are evidence of the effectiveness of the vaccine and of increasing immunity against this disease. The list in adults includes injection site pain and swelling, fatigue, headache, chills, fever, muscle and joint pain, nausea, delayed swelling, redness or a rash at the injection site, swollen lymph nodes (typically manifests as a lump in the armpit or above the collarbone)[11].Most of these reactions should resolve within a few days, according to the U.S. Center for Disease Control and Prevention (CDC)[12].Serious adverse events after COVID-19 vaccination are rare and include anaphylaxis, thrombosis with thrombocytopenia syndrome after receipt of Ad26.COV2.S [13], and myocarditis, myopericarditis, pericarditis,syncope,severe allergic reactions, urticaria and hematologic autoimmune phenomena after receiving mRNA COVID-19 vaccines[14,15].

Menstrual irregularities following COVID-19 vaccine

Interestingly, a growing number of women have reported menstrual irregularities after receiving COVID-19 vaccines. Those observations had been noted in post-authorization and post-licensure monitoring [16]. Menstrual disturbances were reported at frequencies not seen in previous vaccination campaigns [17]. Symptoms related to menstruation and vaginal bleeding were not addressed in the preceding clinical vaccine trials neither were they listed as prespecified symptoms in a v-safe, a voluntary active surveillance system monitoring health status after COVID-19 vaccination in the USA [16,18].

Abnormal uterine bleeding is a common problem in premenopausal women and refers to uterine bleeding that is abnormal in frequency, duration, volume, and/or regularity [19]. There are many factors that can affect menstrual cycles, including stress, endocrine, gynecological, autoimmune, nutrition, genetics, infection, and changes in lifestyle [20].

In many women, menstrual cycle irregularities were observed during the pandemic period. In recent studies, it was observed that SARS-CoV-2 infection itself, COVID-19 vaccines, and also stress in the pandemic may affect the menstrual cycle [21-23].

Women reported disturbances such as altered cycle length, heavier bleeding, and heavy and painful menstruation following COVID − 19 vaccination [24-26]. The adverse events and menstrual irregularities have been reported independent of the type of vaccine used [24-26,27]. However, according to MECOVAC survey, menstrual irregularities normalize within two months in about half of cases [24,28].

Spontaneous reporting systems have also received reports of vaginal bleeding after menopause following COVID-19 vaccination [29,30].

In general, postmenopausal bleeding is vaginal bleeding that occurs a year or more after last menstrual period. It can be a symptom of vaginal dryness, polyps, or other changes in reproductive system. In about 10% of women, bleeding after menopause is a sign of uterine cancer. Postmenopausal bleeding is considered as important medical event [31,17] and the women should seek a gynecologist for full examination and further evaluation.

Additionally, a substantial part of the female population considered as non-menstruating are those who use long-term hormonal contraception. Only few studies have addressed altered bleeding pattern following COVID-19 vaccination in this group of women [32,33].

International effort to study the link between COVID-19 vaccines and menstrual irregularities/vaginal bleeding

For the purpose of this study, we looked into several studies investigating the effect of COVID-19 vaccines and menstrual irregularities/vaginal bleeding that had been published worldwide.

The Norwegian Institute of Public Health followed several cohorts throughout the pandemic and early performed a systematic data collection of self-reported unexpected vaginal bleeding in non-menstruating women. Blix et al. have investigated the association between COVID-19 vaccines and unexpected vaginal bleeding, i.e., vaginal bleeding in postmenopausal women, unexpected vaginal bleeding in perimenopausal women, and breakthrough bleeding in non-menstruating premenopausal women. Using the data from two large population-based cohorts, the authors observed an increased risk of unexpected vaginal bleeding after COVID-19 vaccination in non-menstruating women across different stages of reproductive life [17].

Among 7725 postmenopausal women, 7148 perimenopausal women, and 7052 premenopausal women 3.3, 14.1, and 13.1% reported having one or several unexpected vaginal bleeding episodes during the last 8 to 9 months, of which approximately 50% were reported to have happened within 28 days of vaccination. In postmenopausal women, the risk of vaginal bleeding was increased two to threefold in the 4 weeks after vaccination, as compared to the prevaccination period. The association with vaccination was slightly stronger in peri- and premenopausal women where the risk was increased three to fivefold. In premenopausal women, the first 4 weeks after a dose of Spikevax was associated with a 32% increased risk as compared to Comirnaty [17].

A small survey of pre- and postmenopausal women carried out in Trinidad and Tobago, found that 11 and 38% of the postmenopausal women reported "menstrual symptoms" after the first and second dose, respectively [34].

In a large American sample recruited from social media, unexpected bleeding after vaccination was reported among 70% of women aged 18 to 45 years using long-acting reversible contraceptives and among 66% of postmenopausal women aged ≥55 years [33].

In another American study, 485,644 women aged ≥55 years were included. 95.4% received a messenger RNA (mRNA) vaccine: 52.4% received BNT162b2 (Pfizer–BioNTech) and 43% received mRNA-1273 (Moderna)[35].During the prevaccination interval (Interval 0), the incidence of postmenopausal bleeding was 0.39% (95% confidence interval [CI], 0.38–0.41), increasing slightly after vaccination to 0.47% during Interval 1 (95% CI, 0.45–0.49), and then decreasing to 0.43% (95% CI, 0.41–0.45) during Interval 2 (2-sided Cochran–Armitage test for linear trend in proportions; P=.004. This study similarly found that vaccination was associated with a change in bleeding that was statistically significant but of a magnitude so small that the clinical impact at the population level is negligible [35].

In a Swedish study 2 946 448 women aged 12-74 years were included [32]. 2 580 007 (87.6%) of 2 946 448 women received at least one SARS-CoV-2 vaccination and 1 652 472 (64.0%) 2 580 007 of vaccinated women received three doses before the end of follow-up. The highest risks for bleeding in women who were postmenopausal were observed after the third dose, in the one to seven days risk window (hazard ratio 1.28 (95% confidence interval 1.01 to 1.62)) and in the 8-90 days risk window (1.25 (1.04 to 1.50)). Risk of postmenopausal bleeding suggested a 23-33% increased risk after 8-90 days with BNT162b2 and mRNA-1273 after the third dose [32]. The adjusted hazard ratio for premenopausal bleeding after vaccination with any dose compared with unvaccinated periods was 1.08 (95% confidence interval 0.90 to 1.30) in the one to seven days risk windows and 1.01 (0.91 to 1.12) for the 8-90 days risk windows. Adjustment for covariates almost completely removed the associations reported in the crude analyses and only a weak association remained after the first dose, limited to the one to seven days risk window [32].

No clear difference in bleeding reports according to vaccine type was reported in Ljung et al and Lee et al. studies [32,33,36]. Alzahrani et al. confirmed that type of vaccination is not associated with an abnormal menstrual cycle [37], as did Alghamdi et al. who found only irregular menses in 0.69% after Pfizer-BioNTech administration and 0.45% of cases after Oxford-AstraZeneca [38].

However, the study from Norwegian Institute of Public Health suggests that the vaccine type may influence the risk of vaginal bleeding. The Spikevax (Moderna) vaccine, which contains a higher mRNA dose (100 μg), was associated with a higher risk of vaginal bleeding than Comirnaty (PFIZER) (30 μg), particularly in premenopausal women [17].

In a study from Saudi Arabia 1066 participants were included [37]. Abnormal menstruation was significantly associated with hypertension (p-value = 0.024), polycystic ovary syndrome (p-value = 0.001), and at least one gynecological condition (p-value < 0.001). However, the multivariate regression analysis showed that menstrual abnormality before receiving the COVID-19 vaccine (OR = 0.09, 95% CI, 0.06 to 0.14, p-value < 0.001) was more likely to be associated with abnormal menstruation after receiving the vaccine. The authors concluded that 55.16% of the participants experienced menstrual problems after being vaccinated against COVID-19 compared to 22.89% of the participants who had no menstrual problems after the vaccination [37].

In a study investigating the prevalence and impact of menstrual abnormalities after the COVID-19 vaccine among females residing within the Middle East and North Africa (MENA), a total of 2269 females were included, with a mean age of 34.3 ± 8.5 years [39]. About 66.3% of participants reported menstrual symptoms post-vaccination, of which 46.7% experienced them after their first dose. However, in 93.6% of participants, the symptoms resolved within 2 months. In this study vaccine type did not significantly influence the incidence of abnormalities (p > 0.05) [39].

Also, a meta-analysis was performed in Saudi Arabia to estimate the pooled prevalence of various menstrual disorders in women after COVID-19 vaccination [39]. Overall, the pooled prevalence of menorrhagia was 24.24 % (pooled prevalence 24.24 %; 95 % CI: 12.8–35.6 %). The pooled prevalence of polymenorrhea was 16.2 % (pooled prevalence: 16.2 %; 95 % CI: 10.7–21.6 %). The pooled prevalence of abnormal cycle length was relatively lower than that of the other disorders (pooled prevalence: 6.6 %; 95 % CI: 5.0–8.2 %). The pooled prevalence of oligomenorrhea was 22.7 % (95 % CI: 13.5–32.0 %). showed that there were no significant associated with age, number of children, marital status, vaccination type, previous history of COVID-19 infection, previous diagnosis including PCOS, thyroid disorders, uterine fibroids, endometriosis, and adenomyosis, stopping or starting any king of contraceptive method, history of coagulation disorders (including bleeding, blood clots, thrombocytopenia, or taking coagulation medication), menstrual cycle length, and duration of menstruation (p > 0.05)[39].

In an American observational study of 62 679 female respondents (1·0% of 5 975 363 female respondents aged ≥18 years) with median age of 37 years were analyzed [16]. Common problems identified included timing of menstruation (70 981 [83·6%] responses) and severity of menstrual symptoms (56 890 [67·0%] responses). Other issues included menopausal bleeding (3439 [4·0%] responses) and resumption of menses (2378 [2·8%] responses). Among the 63 815 respondents who reported menstrual irregularities or vaginal bleeding, most respondents received BNT162b2 9 Comirnaty®; BioNTech and Pfizer) (33 149 [51·9%] respondents) or mRNA-1273 (Moderna) (26 741 [41·9%] respondents) vaccines. Interestingly, respondents submitting reports related to menopausal bleeding were more likely to seek health care than were those submitting reports related to other menstruation and vaginal bleeding issues [16].

In a Norwegian study, the authors estimated the association between vaccination and the occurrence of menstrual disturbances among women aged 18-30 years [40]. In the first cycle after vaccination, the authors observed an increased occurrence of unusually heavy and prolonged bleeding, spot bleeding, interval changes, and increased pain during periods, as compared to the last cycle prior to vaccination. The association with vaccination was strongest for heavy menstrual bleeding increasing from 8% before vaccination to 14-15% after vaccination. There were no significant differences in relative risks according to vaccine type/brand, hormonal contraception status or history of gynecological condition(s)[40].

In this American study the authors analyzed prospectively tracked menstrual cycle data using the application "Natural Cycles." 3,959 individuals were included (vaccinated 2,403; unvaccinated 1,556), U.S. residents aged 18–45 years with normal cycle lengths (24–38 days) for three consecutive cycles before the first vaccine dose followed by vaccine-dose cycles (cycles 4–6) or, if unvaccinated, six cycles over a similar time period [41]. Most of the vaccinated cohort received the Pfizer-BioNTech vaccine (55%) (Moderna 35%, Johnson & Johnson/Janssen 7%). Overall, COVID-19 vaccine was

associated with a less than 1-day change in cycle length for both vaccine-dose cycles compared with prevaccine cycles (first dose 0.71 day-increase, 98.75% CI 0.47–0.94; second dose 0.91, 98.75% CI 0.63–1.19); unvaccinated individuals saw no significant change compared with three baseline cycles (cycle four 0.07, 98.75% CI −0.22 to 0.35; cycle five 0.12, 98.75% CI −0.15 to 0.39). Change in menses length was not associated with vaccination. Hence, the authors concluded that (COVID-19) vaccination is associated with a small change in cycle length but not menses length [41].

Furthermore, the same authors, performed an analysis on menstrual cycle tracking data that was prospectively collected using the digital fertility awareness application, Natural Cycles (Natural Cycles USA Corp, NY, US) within an international sample. In the updated analyses, the sample size was increased to include participants from Europe, Canada, USA, Australia, and New Zealand [42]. 19 622 individuals aged 18-45 years with cycle lengths of 24-38 days and consecutive data for at least three cycles before and one cycle after covid (vaccinated group; n=14 936), and those with at least four consecutive cycles over a similar time period (unvaccinated group; n=4686). The purpose of such update was to provide more generalizable results to a broader population and to compare US findings that covid-19 vaccination is associated with small changes in cycle length during the menstrual cycles when vaccine doses are received and that vaccination is not associated with changes in menses length [42]. In the international sample most people (n=15 713; 80.08%) were younger than 35 years, from the UK (n=6222; 31.71%), US and Canada (28.59%), or Europe (33.55%). Two thirds (9929 (66.48%) of 14 936) of the vaccinated cohort received the Pfizer-BioNTech (BNT162b2) covid-19 vaccine, 17.46% (n=2608) received Moderna (mRNA-1273), 9.06% (n=1353) received Oxford-AstraZeneca (ChAdOx1 nCoV-19), and 1.89% (n=283) received Johnson & Johnson (Ad26.COV2. S). Individuals who were vaccinated had a less than one day adjusted increase in the length of their first and second vaccine cycles, compared with individuals who were not vaccinated (0.71-day increase (99.3% confidence interval 0.47 to 0.96) for first dose; 0.56-day increase (0.28 to 0.84) for second dose). The adjusted difference was larger in people who received two doses in a cycle (3.70 days increase (2.98 to 4.42)). One cycle after vaccination, cycle length was similar to before the vaccine in individuals who received one dose per cycle (0.02-day change (99.3% confidence interval −0.10 to 0.14), but not yet for individuals who received two doses per cycle (0.85-day change (99.3% confidence interval 0.24 to 1.46)) compared with unvaccinated individuals. Changes in cycle length did not differ by the vaccine's mechanism of action (mRNA, adenovirus vector, or inactivated virus). Menses length was unaffected by vaccination. Hence, the authors concluded that Covid-19 vaccination is associated with a small and likely to be temporary change in menstrual cycle length but no change in menses length [42].

Interesting results came from a British study [43]. The authors performed a secondary analysis of a retrospective online survey conducted in the UK in March 2021. In pre-menopausal vaccinated participants (n = 4,989), 18% reported menstrual cycle changes after their first COVID-19 vaccine injection. The prevalence of reporting any menstrual changes was higher for women who smoke, have a history of COVID-19 disease, or are not using estradiol-containing contraceptives. In a second sample including both vaccinated and unvaccinated participants (n = 12,579), COVID-19 vaccination alone was not associated with abnormal menstrual cycle parameters, and no difference was found in the risk of reporting frequent or infrequent cycles, irregular cycles, long period duration (+8 days), heavy periods, or IMB between vaccinated-only participants and the control group (not vaccinated and without a history of COVID-19 disease), while a history of COVID-19 disease was associated with an increased risk of reporting heavier bleeding, "missed" periods, and inter-menstrual bleeding. History of COVID-19 disease was associated with an increased tendency of reporting frequent cycles (<24 days), periods stopping and long period duration (8 + days), and a significant increased risk of reporting heavier flow and IMB. Therefore, the results suggested that a history of COVID-19 disease can, in some cases, lead to abnormal cycle parameters, whereas receiving a COVID-19 vaccine does not [43].

In a small study conducted in Turkey, the total number of the participants was 542. 35.7% of those who had COVID-19 and 15.1% of those who had COVID-19 vaccine reported various menstrual irregularities. Some women complained of shortened or delayed menstrual cycles, while some complained of heavier or lighter bleeding. In this study, the change in the menstrual pattern after COVID-19 infection occurred in the form of a delayed cycle in 17.4% of the participants, shortened cycle in 14%, heavier bleeding in 7.4%, lighter bleeding in 5.8%, shorter period in 2.5%, and longer period in 4.1% [20]. The incidence and the nature of the changes in this study are in concordance with the study of Muharam et al. [44].

In a Canadian/American study 76 women met the inclusion criteria and provided 588 cycles for analysis (227 pre-vaccine cycles, 145 vaccine cycles, 216 post-vaccine cycles) [46]. Although 22% of women subjectively identified changes in their menstrual cycle, there were no significant differences in menstrual cycle parameters (cycle length, length of menses, EOD, and luteal phase length) between the pre-vaccine, vaccine, and post-vaccine cycles. The authors concluded that COVID-19 vaccines were not associated with significant changes in menstrual cycle parameters and that perceived changes by an individual woman must be compared with statistical changes to avoid confirmation bias [45].

A Chinese study published in 2022, analyzed 13,118 reports of menstrual disorders associated with COVID-19 vaccine [46]. To evaluate the potential relationship between COVID-19 vaccine and reports of menstrual disorders the Reporting Odds Ratio (ROR) method was used. The most reported event after exposure to COVID-19 vaccines was menstruation irregularity (4998 reports), and 42.55% of the reported menstrual irregularities were in the group of females aged 30–49 years. In that group there were 2698 cases (20.57%) of menstruation delayed,2088 cases (15.92%) of intermenstrual bleeding reported and menorrhagia was reported in only 28 cases (0.21%). The highest proportion of reports was for the Pfizer-Biontech vaccine, with 1065 reports mentioning serious adverse events. Most reports of menstrual disorders occurred after the first dose of the COVID-19 vaccine, with only about 0.5% reported after the third dose of the vaccine. The interval between vaccination and adverse reaction reporting was within 100 days in 82.92% of patients, but only 18.01% of patients reported that their adverse reactions had vanished, and 62.88% of patients reported that they still had adverse reactions related to vaccination. The authors concluded that reports of menstrual disorder-like events after vaccination of female with the COVID-19 vaccine are age-related, and females of reproductive age between 30- and 49-years old need to pay particular attention to adverse reactions after vaccination [46].

In this American study V-safe system had been employed for data collection [16]. V-safe is an active surveillance system for monitoring COVID-19 vaccination safety administered by the US Centers for Disease Control and Prevention (CDC). Participation in this active surveillance system is open to all people in the USA and its territories who receive a COVID-19 vaccination and who can access v-safe using a smartphone. Respondents self-enroll and receive text-message reminders to complete surveys at specified intervals after vaccination [18].

Among the 63 815 respondents who reported menstrual irregularities or vaginal bleeding, most respondents received BNT162b2 (33 149 [51·9%] respondents) or mRNA-1273 (26 741 [41·9%] respondents) vaccines [16]. Several types of menstrual symptoms were reported, with most being related to disruptions in menstrual timing (83·6%) or increased severity of menstrual symptoms (67·0%), such as bleeding or pain. Some respondents also described symptoms related to perimenopausal and postmenopausal bleeding (4·0%), and resumption of menses after a long period of no menses (2·8%). 57 997 respondents who submitted responses related to menstruation or vaginal bleeding were aged 18–49 years, which included 57 046 female respondents (1·8% of 3 095 361 females aged 18–49 years). 511 respondents

who submitted responses related to menstruation or vaginal bleeding were aged 65 years and older, which included 434 female respondents (<1% of 1 181 482 female individuals aged 65 years and older) [16].

The Italian study published the results of the MECOVAC survey [24]. According to their data analysis, approximately 50–60% of reproductive-age women who received the first dose of the COVID-19 vaccine reported menstrual cycle irregularities. Moreover, the authors did not find significant differences ($p = 0.60$) between recombinant (Vaxzevria and Janssen) and mRNA vaccines (Comirnaty and Moderna). The occurrence of menstrual irregularities seems to be slightly higher (60–70%) after the second dose. Menstrual irregularities after both the first and second doses of the vaccine were found to self-resolve in approximately half the cases within two months [24].

In a Lebanese study published in 2023, in the cohort of 505 women the authors observed that following vaccination, the number of women having heavy bleeding or light bleeding increased ($p = 0.02$ and $p < 0.001$, respectively) [47]. The number of women having regular cycles decreased after taking the vaccine ($p < 0.001$). Irregularity in the cycle post-vaccination was associated with worse PMS symptoms ($p = 0.036$). Women using hormonal contraception method or using any hormonal therapy had higher menstrual irregularity rates ($p = 0.002$ and $p = 0.043$, respectively). Concerning vaccine adverse events, those who had headaches had a higher rate of irregularity ($p = 0.041$). Those having PCOS, osteoporosis, or blood coagulation disorders had higher irregularity rate ($p < 0.001$ and $p = 0.005$, respectively) [47].

It is of interest, that in this study the authors observed that irregular cycles were associated with worse PMS symptoms. The physio pathological mechanism of PMS can be explained by the endocrine system alterations [48], which may be caused by the cycle irregularity. The heavy bleeding experienced by many participants can also be a contributor to a worse PMS [47,49].

A descriptive-analytical cross-sectional study was performed in 427 female participants working as part of a medical care team in seven selected hospitals in Tehran, Iran [50]. 157 (36.1%) reported a history of COVID-19 with a positive PCR test. Also, 203 (46.6%) had received Sinopharm vaccine, 116 (26.6%) AstraZeneca vaccine, 80 (18.8%) SputnikV vaccine and 34 (8%) Covaxin vaccine. The study showed that 8% of women's Sinopharm vaccine, 10.7% for AstraZeneca vaccine, 5% receiving SputnikV vaccine, and 17.6% of women receiving Covaxin reported menstrual irregularities (hypermenorrhea-dysmenorrhea menorrhea). The difference between the effects of these four types of vaccines on menstruation via the Chi-Squared test showed a significant difference among all of them (P=0.01). The most commonly vaccine-induced change in menstruation was reported for Covaxin (17.6%), while the least change was recorded for SputnikV (5%). And, accordingly, AstraZeneca (10.7%) and Sinopharm (8%) vaccines ranked second and third. Overall, the most common complication (in terms of number) was menstruation disturbances (38 cases (8.8%), followed by metrorrhagia, 20 cases (4.6%), and finally, 7 cases (1.6%) of hirsutism. In this study, Covaxin revealed the most side effects in terms of menstruation disturbances [50].

The authors of another American study investigating the phenomenon of changed menstrual bleeding patterns were using a web-based survey with a cohort of 39,129 respondents in the sample [33]. The participants were between 18 and 80 years old (median = 33 years; Mage = 34.22 years, SD = 9.18) and were fully vaccinated (at least 14 days after one or two required doses as this was before boosters) additionally, had not contracted COVID-19 (diagnosed or suspected). Respondents were vaccinated with Pfizer (N = 21,620), Moderna, (N = 13,001), AstraZeneca (N = 751), Johnson & Johnson (N = 3469), Novavax (N = 61), or other (N = 204) vaccines, with 23 not reporting vaccine type.

In total, 42.1% reported heavier menstrual flow after vaccines, 14.3% reported not heavier (characterized by a mix of lighter or no change) menstrual flow, and 43.6% reported no change to flow after vaccines [33].

Among respondents who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones, and 66% of postmenopausal people reported breakthrough bleeding. Increased/breakthrough bleeding was significantly associated with age, systemic vaccine side effects (fever and/or fatigue), history of pregnancy or birth, and ethnicity. Interestingly, age was significantly different between those that experienced breakthrough bleeding occurrence or not [$t(147.99) = -2.255$, $P = 0.026$], with postmenopausal people who experienced breakthrough bleeding being slightly younger (M = 59.8 years) than those who did not (M = 61.4 years). Ethnicity was associated with breakthrough bleeding, with non-Hispanic/Latinx respondents being less likely to report breakthrough bleeding. There was no significant difference in rate of occurrence of breakthrough bleeding by vaccine type, systemic side effects of fever or fatigue, or reproductive history of past pregnancy or parity [33].

A systematic review and meta-analysis to review and quantify the impact of COVID-19 vaccinations on the menstrual cycles of women of reproductive age, was performed by a Canadian/Swiss group and published in 2022 [51].

They included four articles in their systematic review and meta-analysis. The articles described 19,019 women of reproductive age in the vaccinated (exposed) group and 6,045 women of reproductive age in the unvaccinated (unexposed) group, for a total of 25,054 women [51]. The pooled OR is 1.91 (CI: 1.76–2.07), indicating an association between vaccination and menstruation changes. The statistical analysis results indicate heterogeneity between the studies and the dispersion of values is statistically significant ($\chi 2 = 195.0$ with $df = 3$, $p < 0.00001$, $I2 = 98\%$). The overall effect of the mean was statistically significant ($Z = 16.01$, $p < 0.0001$), therefore these findings contribute to a growing body of evidence surrounding potential changes in menstrual cycles [51].

The menstrual cycle is an important part of a woman's life. A normal menstrual cycle is an indicator of good health, and disturbances in the menstrual cycle can indicate underlying conditions [52]. In general, changes to menstrual bleeding are not uncommon, but the providers should take time to talk to patients about the link between vaccination and menstrual changes as unexplained side effects in form of changes to a women menstrual cycle could be concerning and even frightening. Additionally, women should be reassured that those menstrual changes are not a cause for concern for long-term physical or reproductive health.

Moreover, it is important to understand that findings of menstrual irregularities following COVID-19 vaccination are relevant to the worldwide trend of vaccine hesitancy and may provide fuel for anti-vaccination campaigns [51].

Vaccine hesitancy it is a worldwide problem and The World Health Organization in 2019 has identified vaccine hesitancy as one of the top ten threats to global health [53]. Therefore, counseling patients with regards to possible post-vaccination menstrual cycle changes is quite essential as the realization will reduce the unnecessary anxiety that is experienced by women due to menstrual irregularities.

Biologically plausible link between COVID-19 vaccination and menstruation

It is well known that the hypothalamic–pituitary–ovarian axis which regulates the timing and length of the menstrual cycle can be affected by various biological and environmental factors [54-58]. Individual variability in cycle length is common [59,60], and a change in cycle length of <8 days is considered normal [61].

However, even changes considered clinically normal, when unexplained, can be concerning and causing anxiety [62-64]. Right now, the hypothesis that

menstrual irregularities occurred due to COVID-19 pandemic stress rather than the vaccination itself also cannot be ruled out based on available evidence [54].

However, studies have shown similar results across COVID-19 vaccine types (mRNA, adenovirus-vector, and inactivated), indicating that the most likely mechanism is through activation of the immune system, rather than any specific component of the vaccine itself [42,65,66]. Indeed, cytokine production as part of the immune response to vaccination may temporarily interfere with the hypothalamic–pituitary–ovarian axis and production of ovarian hormones responsible for controlling menstrual function [67-69].

Post-vaccine systemic inflammatory reactions could disrupt menstruation [69] and trigger breakthrough bleeding [16]. Manual review of v-safe responses suggested some reports of breast tenderness, mood changes, and tinnitus; these symptoms could be related to hormonal changes, which could disrupt normal menstruation, menopause, or pre-existing amenorrhea secondary to medications or other medical conditions [16]. Menstrual cycle prolongation has been associated with receiving two COVID-19 vaccine doses within the same cycle [41], supporting the hypothesis that immune response to vaccination can affect the hypothalamic–pituitary–ovarian axis [16]. Additionally, short lived menstrual irregularities have been reported after SARS-CoV-2 infection [71,72].

The intense immune response after SARS-COV-2 infection, and similarly to the administration of COVID-19 vaccines, could be a potential stressor that changes the hypothalamic–pituitary–ovarian axis or a possible direct effect of the virus. Similar pathophysiology might underlie the occurrence of menstrual irregularities after COVID-19 vaccination [16,68,73,54]. The COVID-19 pandemic caused stress and evoked negative emotions like fear, anxiety, boredom, irritation, adjustment disorder and frustration, which all could increase incidence of menstrual irregularities [74,75].

However, one of the causes of menstrual irregularities is thought to be the effect of the virus itself. The SARS-CoV-2 virus makes its way into the cell by binding to the ACE2 (angiotensin-converting enzyme 2) receptor which presence on ovarian follicles has now clearly been established and expression of ACE 2 receptors on the ovarian follicles is essential for maturation of these follicles along with ovulation, modulation of luteal angiogenesis and degeneration, and it also influences the regular changes which are observed in endometrial tissue and embryo development [20,76].

Angiotensin II is essential for regular menstrual cycles and alteration in the receptors of angiotensin II may thus lead to dysfunctional uterine bleeding and hyperplasia of the endometrium [77]. The role of ACE2 receptors in the endometrium is manifested in the involvement of angiotensin II in the initiation of menstruation through vasoconstriction of the spiral artery and angiotensin II-mediated increase in the proliferation of uterine epithelial cells. Therefore, the interaction between SARS-CoV-2 and ACE2 receptors in the endometrium may be among the causes of post infection menstrual changes [20,77,78].

Additionally, studies have shown that cytokines such as interleukin-6, interleukin-8, and tumor necrosis factor-alpha, which are the mediators of the inflammatory response in COVID-19, can trigger a procoagulant state, resulting in changes in the menstrual pattern and in the amount of bleeding following infection [20,79,80].

There is also another plausible hypothesis for post-vaccination menstrual changes, which could be immune-mediated vaccine-induced thrombocytopenia, a phenomenon that has previously been observed resulting from vaccination with several other vaccines such as measles, hepatitis, and diphtheria vaccines [81,82].

Conclusion

Conclusions regarding the impact of COVID-19 vaccination on female menstrual cycles can only be drawn once more high-powered studies would be available [54].

The importance of the issue has been recognized by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency which decided to list heavy menstrual bleeding as a side effect as a side effect of unknown frequency in the product information for the SARS-CoV-2 mRNA vaccines [83]. The recommendation follows a review of the available evidence, including cases reported during clinical trials, cases spontaneously reported in Eudravigilance, and findings from the medical literature [83]. The Committee emphasized that there is no evidence to suggest that above mentioned menstrual disorders have any impact on reproduction and fertility and available data provides reassurance about the use of mRNA COVID-19 vaccines before and during pregnancy [83].

Disclosure

The authors report no conflict of interest.

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