Does side effects of COVID-19 vaccination include changes in menstrual cycle or its associated pre- and post-menstrual symptoms in reproductive-age women: A Multi-centric Observational study in India.

Naina Kumar[1], Neha Gagane[2], Ipsita Mahopatra[3], Charushila Rukadikar[4], Vijayan Sharmila[5], K. Pushpalatha[2], Madhavi Eerike[1], G. Santhoshi[1], Subha Samantaray[3], Shikha Seth[4], Pragati Trigunait[5], Nanditha Reddy[5], Shweta Patel[2], Sandhya Rani[1], Roopanshi Mishra[4], and Kamlesh Negi[4]

[1]All India Institute of Medical Sciences - Bibinagar
[2]All India Institute of Medical Science - Bhopal
[3]All India Institute of Medical Sciences - Kalyani
[4]All India Institute of Medical Sciences - Gorakhpur
[5]All India Institute of Medical Sciences - Mangalagiri

January 14, 2023

Abstract

Objective: The study was conducted to know the impact of COVID-19 vaccination on menstrual cycle patterns, pre- and post-menstrual symptoms in women aged 18-45 years. Design & Setting: Multicentric observational study conducted in six institutes of national importance in different states of India over one year. Population: A total of 5709 female participants fulfilling inclusion criteria were enrolled. Methods: Data about impact of vaccines (COVISHIELD and COVAXIN) and prior COVID-19 infection on menstrual cycle and its associated symptoms were obtained using an online and offline survey. Main Outcome: COVID-19 vaccination with COVISHILED/COVAXIN resulted in menstrual cycle disturbances. Results: Of 5709 participants, 78.2% received COVISHIELD, 21.8% COVAXIN. Of all, 333(5.8%) developed post-vaccination menstrual disturbances with 32.7% frequent cycles, 63.7% prolonged cycles, and 3.6% inter-menstrual bleed. 301 participants, noticed changes in the amount of bleeding, with 50.2% excessive, 48.8% scanty, and 0.99% amenorrhea followed by heavy bleeding. Furthermore, the irregularities of menstrual cycle (p=0.011) and length (0.001) were significantly higher in the COVAXIN group (7.2%) as compared to COVISHIELD (5.3%). A total of 721 participants complained of newly developed/worsening pre- and post-menstrual symptoms. These symptoms were significantly higher in COVISHIELD group (p=0.031) with generalized weakness and body pains as main complaints (p=0.001). No significant difference was observed in COVID-19 infection incidence with these vaccines. When comparing menstrual abnormalities among those with COVID-19 infection, no significant associations were observed (p >0.05). Conclusions: COVISHILED and COVAXIN resulted in menstrual cycle disturbances and pre-and post-menstrual symptoms. The menstrual irregularities were significantly higher with COVAXIN vaccine.

Introduction

COVID-19 infection started in December 2019, and since then it has affected almost every aspect of lives globally. Studies have reported that COVID-19 infection can affect every human organ including reproductive organs causing widespread inflammation, vasoconstriction, hypercoagulability, and edema.[1-3] To combat this dreadful disease, numerous vaccines were introduced within a short span of 12-18 months of the onset of

the pandemic.[4] The adult vaccination against COVID-19 started at the end of 2020 and early 2021 worldwide and around three billion doses were administered globally by mid-2021, hoping to end this pandemic at the earliest.[5] The two indigenously developed COVID-19 vaccines approved for use in India are COVISHILED and COVAXIN.[6] The common side effects of these vaccines included injection site pain, fever, and myalgia with no severe adverse effects.[7] The common side effects of other COVID-19 vaccines used in different countries were soreness of the arm, fever, chills, myalgia, headache, fatigue, and rarely thrombosis and anaphylaxis.[8,9] Recent studies from the United States of America and other countries have reported temporary changes in the menstrual cycle including increased cycle length, and dysmenorrhea following COVID-19 vaccination.[10,11]

Most of the reproductive age women suffer from some kinds of premenstrual symptoms including physical discomfort, mood changes, body pains, etc. Of these 5–8% suffer from a severe premenstrual syndrome that affects their day-to-day activities.[12] The menstrual cycle reflects the general health status of women and should be considered a vital sign of health.[13] Despite this, the impact of COVID-19 vaccines on the menstrual cycle in women and girls getting vaccinated against COVID-19 infection was not considered and hence, not included in the list of side effects.[14]The present study was the first of its kind in India that was conducted on a large sample from different states of India to investigate the impact of COVID-19 vaccination on the menstrual cycle and pre- and post-menstrual symptoms in women of the reproductive age group and to establish the correlation with the vaccine type.

Materials and Methods

Study design: Multicentric observational study.

Study setting and duration: The present study was conducted in six institutes of national importance [All India Institute of Medical Sciences (AIIMS) Hyderabad; AIIMS, Mangalagiri; AIIMS, Nagpur; AIIMS, Kalyani; AIIMS, Gorukhpur; and AIIMS, Bhopal] in different states of India over one year.

Study Population

Inclusion criteria: All female participants between 18-45 years of age who had received two doses of either COVISHIELD or COVAXIN vaccine with or without a booster dose and had previous 3 regular cycles before vaccination were enrolled as study participants. They were enrolled after [?]2 months since their last dose and up to 8 months post-vaccination. The flow chart below depicts enrollment of participants at different centers and the collection of data for analysis and compilation.

Exclusion criteria: All females <18 years or >45 years, those who were unvaccinated or not fully vaccinated, had previously irregular cycles, pregnant, immediate postpartum or post-abortal, lactating, on hormonal or IUCD contraceptives, anticoagulants/antipsychotic drugs, currently suffering from COVID-19 infection, with co-morbidities like diabetes, thyroid disorders, hyperprolactinemia, tuberculosis, autoimmune diseases, morbidly obese, acutely ill patient and those not willing to be a part of the study were excluded.

Operational definitions

Normal menstrual cycle: A normal menstrual cycle is regular, and has a frequency of 24-38 days, occurring for 7 days, with 5-80 ml blood loss.[15]

Premenstrual syndrome: It includes clinically significant somatic and psychological manifestations occurring during the luteal phase of the cycle, causing considerable distress and impairment in functional capacity.[16]

Fully vaccinated against COVID-19 infection: According to the Centers for Disease Control and Prevention (CDC) individuals who have received their primary series (two doses of COVID-19 vaccine) are considered fully vaccinated after two weeks of their second dose, irrespective of booster doses.[17]

Not Fully vaccinated against COVID-19 infection: Those who received a second dose less than 2 weeks ago or those who didn't receive their second dose of a two-dose vaccine.[17]

Sample size : Sample size was calculated assuming that 50% of the subjects in the population had the factor of interest, with a design effect of two and an expected response rate of 80%, as 961 (with 5% absolute precision, 95% confidence and failure to a response rate of 10%). Since six centers were included as a part of the study, so a total of 5766 sample size was considered. The sample size was calculated using a free online statistical calculator (statulator).[18]

Sampling method: Consecutive sampling was done till the desired sample size of 961 was achieved at each center.

Flow chart

Study Tool

The study was conducted using a printed data collection sheet for female patients reporting to the outpatient departments of various specialties for different complaints and a similar online-based questionnaire created through Google Forms online survey development software was used for the hospital staff, students, and faculty members at each institute. The questionnaire was first developed in English and then translated into Hindi, Telugu, Marathi, and Bengali by a translating expert. The questionnaire was then validated by faculties from different departments for its language, content, and completeness.

The questionnaire consisted of detailed questions covering seven important domains (Supplementary file). The first was related to demographics, including age, marital status, religion, residential address, education, occupation, socio-economic status, age at menarche, and the number of children (9 questions). The second section had questions related to contraception and its details (3 questions), and the third section was on pre-vaccination menstrual cycle details (5 questions). The fourth section had details of COVID-19 vaccination including the type of vaccine, number of doses and their dates, and the booster dose (4 questions). The fifth section dealt with post-vaccination menstruation details (7 questions), and the sixth category was on the history of COVID-19 infection and its details including time of infection (before, during, or after completion of COVID-19 vaccination schedule), severity, need for hospitalization and its impact on menstrual cycle (5 questions). The seventh category consisted of open and close-ended questions related to physical examination (height and weight), medical and surgical history, history of stress, excessive weight gain or loss, and vigorous exercise in the past 6 months (6 questions).

A pilot study was conducted to check for the validity and reliability of the questionnaire on 20 participants to find any flaws or missing questions. Accordingly, the questionnaire was reviewed again by a group of faculties from the Department of Obstetrics and Gynecology at the coordinating center to further ensure the validity of the questionnaire prior to the initiation of the survey. These 20 participants were excluded from the main study and subsequent analyses.

Data Collection

After explaining the survey, and informed written consent, a face-to-face interview of all the female patients fulfilling inclusion criteria and reporting to the outpatient department complex was conducted by trained nursing staff. Google forms were circulated amongst all hospital female staff, students, and faculties for their responses. The google forms also had a participant information sheet including a privacy and confidentiality statement and consent form to be filled out prior to attempting the survey. Only those fulfilling the inclusion criteria as observed from the google form responses of the participants were analyzed, while others were excluded from the analysis (57 participants not fulfilling the inclusion criteria were excluded from the study).

Statistical Analysis

The data was statistically analyzed by Statistical Package for the Social Sciences (SPSS) software version 21.0. The numerical data were presented as percentages or mean ± standard deviation (SD) and categorical variables as frequencies or rates where ever needed. ANOVA/Kruskal Wallis test was used for the comparison of more than two groups and the Chi-Square test for a comparison of qualitative variables. A p-value of <0.05 was considered statistically significant.

Ethical Issues

The present research involving human subjects was conducted following the ethical standards of all applicable national (ICMR National Bioethical Guidelines 2017) and institutional committees and the World Medical Association's Helsinki Declaration. It was conducted after informed written consent from the participants and ethical approval from the Institutional Ethical Committee of all the six centers of India included in the study (IEC numbers: AIIMS/BBN/IEC/APR/2021/24; AIIMS/MG//IEC/2022-23/198; IEC/AIIMS/KALYANI/2022/12; IEC/Pharmac/2022/416; IHEC/AIIMS-GKP/BMR/111/2022; IHEC-LOP/2022/EL043;).

Results

Socio-demographic and clinical parameters

Out of the total 5766 participants surveyed, 5709 fulfilled the inclusion criteria and hence were analyzed. The majority of the participants (44.2%) belonged to >25-[?]35 years of age with the mean age of all the participants as 29.12+-7.12 years. The majority of the participants were married (67.3%), Hindu by religion (87.9%), unemployed (42.0%), and belonging to lower middle socio-economic status (55.7%). The mean age of menarche and parity for all the participants was 13.09+-1.07 years and 0.88+-1.06 respectively. Of all the participants, 88.9% were currently not using any method of contraception, while 11.1% were either using barrier methods (6.1%) or underwent permanent family planning operations (5.0%). The details of various socio-demographic features of all the participants are depicted in Table 1. The mean+-SD of weight, height, and body mass index (BMI) of all the participants was 57.24+-9.24 Kg, 155.44+-6.29m, and 23.76+-4.04Kg/m^2 respectively.

All the enrolled participants had regular cycles (28-30 days), with a moderate amount of bleeding lasting for an average duration of 4.66+-1.38 days prior to vaccination, as this was one of the inclusion criteria for the study.

Vaccination details

Of the total 5709 participants, 4464(78.2%) received COVISHIELD, while 1245(21.8%) received COVAXIN vaccination against COVID-19 infection. Only 14.6% (833/5709) received a booster dose for COVID-19 infection.

Post-vaccination menstrual cycle and associated pre- and post-menstrual symptoms

Of the total 5709 participants, 333(5.8%) developed irregularities of the menstrual cycle with 32.7% (109/333) having frequent cycles (every [?]20 days), 63.7% (212/333) prolonged cycles (>38 days), and 3.6% (12/333) intermenstrual bleed. A total of 301 out of 5709 participants (5.3%), noticed changes in the amount of bleeding during menstruation, with 151(50.2%) having excessive bleeding, 147(48.8%) scanty bleeding lasting for an average of 1-2 days with 0-1 pads/day, and the remaining three participants (0.99%) had amenorrhea for 3-5 months followed by heavy bleeding. Of these 301 participants, 130 (43.2%) had both irregular cycles with changes in the amount and duration of bleeding. The remaining 5408 (94.7%) participants observed no change in the amount of bleeding during menstruation post-vaccination. Furthermore, the irregularities of the menstrual cycle were significantly higher (p=0.011) in the COVAXIN group (7.2%) as compared to women who received the COVISHIELD vaccine (5.3%). Of the total of 1245 women who received the COVAXIN vaccine, 3.2% complained of frequent cycles (every <20 days) and 4.3% prolonged cycles (>38 days), which was significantly higher than the women who received the COVISHIELD vaccine (p=0.001). The mean+-SD duration of bleeding and the number of sanitary pads used per day during menstruation in all the participants post-vaccination was 4.69+-1.54 days, and 3.39+-1.10 respectively. A total of 449(7.9%) participants observed the new onset passage of clots during menstruation. No statistically significant difference (p=0.346) was observed in the mean duration of bleeding pre- and post-vaccination in both the vaccine groups as depicted in Figure 2. A total of 721 (12.6%) participants complained of newly developed or worsening pre- and post-menstrual symptoms including severe dysmenorrhea with or without diarrhea (55.3%), severe lower backache (9.4%), lower abdominal dragging pain (18.0%), generalized

weakness and body aches (8.9%), vaginal pain (1.7%) and increased vaginal discharge (0.7%) along with some non-specific symptoms in 5.96% participants including genital itching, burning sensation in the vagina during menses, increased hair loss, increased appetite, and insomnia during menstrual cycles. New onset or worsening of pre- and post-menstrual symptoms were significantly higher in the COVISHIELD group (p=0.031) with generalized weakness and body pains as the main complaint (p=0.001). The comparison of menstrual cycle patterns, and associated pre- and post-menstrual symptoms between women who received COVISHIELD and COVAXIN vaccines is depicted in Table 2.

COVID-19 infection before, during, or after vaccination

A total of 721(12.6%) participants suffered from COVID-19 infection before, during, or after the completion of two doses of vaccines. Of these 721 participants, 326(45.2%) had COVID-19 infection before vaccination, 83(11.5%) during vaccination (after the 1st dose, but before 2nd dose of vaccination), 307(42.6%) after completion of 2 doses of vaccination, and five (0.7%) during and after completion of vaccination (Table 3). A total of 584(81.0%) participants out of 721 received the COVISHIELD vaccine and the remaining 137(19.0%) had the COVAXIN vaccine. No significant difference was observed in the incidence of COVID-19 infection during and after vaccination with either COVAXIN or COVISHIELD vaccines (p=0.236).

Post-COVID-19 infection menstrual cycle pattern and pre- and post-menstrual symptoms

A total of 47(6.5%) participants of 721 who had a history of COVID-19 infection observed changes in their menstrual cycle post-infection. Of these 47 participants, 25(53.2%) observed change in the amount of bleeding (17 having excessive bleeding, of which eight had bleeding lasting for >7 days, and the remaining nine participants complained of scanty menses), 22(46.8%) complained of changes in the cycle length, and 19(40.4%) observed the new onset passage of clots during menses which was not there before the infection. Furthermore, 15(5.5%) participants complained of new-onset severe dysmenorrhea and or burning sensation in the vagina during menstruation. Table 3 depicts the comparison of COVID-19 infection onset and severity, post-infection menstrual cycle changes, and its associated symptoms in women who received COVISHIELD or COVAXIN vaccines. When comparing menstrual abnormalities including length of cycle, and amount of bleeding among those with a history of COVID-19 infection before, during, or after vaccination, no significant associations were observed (p >0.05).

Discussion

The present study included 5709 participants, with 4464(78.2%) having received COVISHIELD, and 1245(21.8%) had COVAXIN against COVID-19 infection. Of the total 5709 participants, 333(5.8%) developed post-vaccination irregularities of menstruation with 32.7% having frequent cycles (every [?]20 days), 63.7% prolonged cycles (>38 days), and 3.6% inter-menstrual bleed. A total of 301 participants (5.3%), noticed changes in the amount of bleeding during menstruation, with 50.2% having excessive, 48.8% scanty bleeding, and 0.99% had amenorrhea followed by heavy bleeding. Furthermore, the irregularities of the menstrual cycle (p=0.011) and cycle length (0.001) were significantly higher in the COVAXIN group (7.2%) as compared to the COVISHIELD vaccine (5.3%). No significant difference was observed in the duration and amount of menstrual bleeding in the two vaccine groups (p>0.05). A total of 721 (12.4%) participants complained of newly developed or worsening pre- and post-menstrual symptoms. These symptoms were significantly higher in the COVISHIELD group (p=0.031).

Similar results of the impact of COVID-19 vaccination on menstrual cycles were reported by other studies from all across the world. A study conducted on 950 women to know the impact of COVID-19 vaccination on the menstrual cycle, reported changes in frequency (normal 43.47%, infrequent 25%, and frequent 31.53%), regularity (regular 51.08%, irregular 42.93%, and absent/amenorrhea 5.97%), duration (normal 65.21%, prolonged 26.08%, absent/amenorrhea 8.69%), and volume (heavy 41.84%, light 20.65%, and amenorrhea 6.52%) of menstruation in 184 women out of 408 fulfilling the inclusion criteria. It was concluded that COVID-19 vaccination can influence the menstrual cycle and cause alterations.[19] A recent cross-sectional study from the Middle East and North Africa was conducted on 2269 females fully vaccinated against COVID-19 infection to assess the impact of vaccines (AstraZeneca, Sinopharm, and Pfizer) on menstrual abnormalities

and reported that 66.3% of participants reported abnormal menstrual symptoms post-vaccination with the resolution of these symptoms within 2 months in 93.6% of participants. Similar to our study it was observed that vaccine type did not significantly affect the incidence of abnormalities ($p > 0.05$). Furthermore, they also reported that participants with confirmed previous COVID-19 infection had a similar percentage of menstrual abnormalities compared to those who did not have COVID-19 infection. Hence, it was concluded that women subjected to COVID-19 vaccines experienced menstrual abnormalities including, longer menstruation duration and increased menstrual cycle lengths.[20]

Another cohort study was conducted in the United States of America on 3,959 women (vaccinated 2,403; unvaccinated 1,556) to assess the association between COVID-19 vaccination (Pfizer-BioNTech, Moderna and Johnson & Johnson/Janssen vaccines) and changes in menstrual cycle length. It was observed that the COVID-19 vaccine was associated with a < 1-day change in cycle length compared to pre-vaccine cycles. Hence, it was concluded that COVID-19 vaccination was associated with only a small change in the cycle length but not the duration of menstrual bleeding.[11] Another similar study was conducted on 19,622 women between 18-45 years of age to know whether the COVID-19 vaccines (Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Johnson & Johnson) were associated with menstrual changes. It was reported that vaccinated women had a < 1-day adjusted increase in the cycle length as compared to the unvaccinated ones. Furthermore, it was observed that the adjusted difference was larger in women who received two doses. Hence, it was concluded that COVID-19 vaccination was associated with a small and temporary change in the menstrual cycle length without affecting the bleeding duration.[21] A similar recent study was conducted on 9,652 women (8,486 vaccinated; 1,166 unvaccinated) to know the impact of COVID-19 vaccines on the menstrual cycle length. All the participants were followed for 10 cycles and it was found that the vaccinated women had a small increase in mean cycle length. It was concluded that COVID-19 vaccination was associated with an immediate short-term increase in menstrual cycle length.[22]

Very few studies have been conducted to know the impact of COVID-19 vaccination on pre-and post-menstrual symptoms. A recent questionnaire-based study compared menstruation characteristics (regularity, volume, intermenstrual bleeding, and dysmenorrhea) before and after receiving the COVID-19 vaccine in Saudi Arabia and reported a significant impact of COVID-19 vaccination on menstrual disturbances.[23]

In the present study a total of 721(12.6%) participants suffered from COVID-19 infection before, during, or after the completion of vaccination. Of these, 584(81.0%) participants received the COVISHIELD vaccine and the remaining 137(19.0%) had the COVAXIN vaccine ($p=0.236$). No significant difference was observed in the incidence of COVID-19 infection with either COVAXIN or COVISHIELD vaccines ($p>0.05$). When comparing menstrual abnormalities including cycle length, and amount of bleeding among those with a history of COVID-19 infection before, during, or after vaccination, no significant associations were observed ($p >0.05$). A similar study was conducted on 483 women from Jordan and Iraq to evaluate menstrual changes in women post-COVID-19 infection. It was reported that 47.2% of women suffered from a change in the number of days between two consecutive cycles, and a change in the amount of bleeding during menses post-infection. Hence, it was concluded that COVID-19 infection may affect the menstrual cycle pattern in females.[24]Similar results of menstrual cycle disturbances in women post-COVID-19 infection have been reported by other studies[25-27], but still, further research is necessary for better evidence and conclusion.

Strengths & Limitations

The study was the first of its kind in India, conducted on a large sample to investigate the impact of two vaccines approved for use in India on the menstrual cycle pattern in reproductive-age women.

The major drawback of the study was, it failed to compare vaccinated with unvaccinated women as by the time it started the majority of females were either partially or fully vaccinated. In the future, we may plan to conduct a long-term follow-up of women reporting changes in their menstrual cycle after vaccination or COVID-19 infection to know for how long these irregularities lasted and to establish the cause-effect relationship with the vaccination.

Conclusion

COVID-19 vaccination with COVISHILED and COVAXIN resulted in menstrual cycle disturbances including changes in cycle length, duration, and amount of bleeding and pre-and post-menstrual symptoms. Menstrual cycle irregularities including length were significantly higher in the COVAXIN group, whereas pre-and post-menstrual symptoms were more commonly observed with the COVISHIELD vaccine. No significant difference was observed in the incidence of COVID-19 infection in either group. Furthermore, no significant association was found between COVID-19 infection and menstrual cycle changes. Hence, COVID-19 vaccines can affect menstrual cycle patterns and lead to new-onset pre- and post-menstrual symptoms in women, but for what duration these changes will last post-vaccination need to be further evaluated.

References

1. Jain U. Effect of COVID-19 on the Organs. Cureus. 2020;12(8):e9540. doi: 10.7759/cureus.9540.
2. Li R, Yin T, Fang F, Li Q, Chen J, Wang Y, et al. Potential risks of SARS-CoV-2 infection on reproductive health. Reprod Biomed Online. 2020;41(1):89-95. doi: 10.1016/j.rbmo.2020.04.018.
3. Carneiro Gomes PR, Rodrigues da Rocha MD, da Rocha Coelho FA, Sousa Pinho de Lira JA, de Sousa Carmo RR, Silva Nascimento HM, et al. Alterations of the male and female reproductive systems induced by COVID-19. Wien Klin Wochenschr. 2021;133(17-18):966-972. doi: 10.1007/s00508-021-01875-2.
4. Bok K, Sitar S, Graham BS, Mascola JR. Accelerated COVID-19 vaccine development: milestones, lessons, and prospects. Immunity. 2021;54(8):1636-1651. doi: 10.1016/j.immuni.2021.07.017.
5. Ndwandwe D, Wiysonge CS. COVID-19 vaccines. Curr Opin Immunol. 2021;71:111-116. doi: 10.1016/j.coi.2021.07.003.
6. Behera P, Singh AK, Subba SH, Mc A, Sahu DP, Chandanshive PD, et al. Effectiveness of COVID-19 vaccine (Covaxin) against breakthrough SARS-CoV-2 infection in India. Hum Vaccin Immunother. 2022;18(1):2034456. doi: 10.1080/21645515.2022.2034456.
7. Parida SP, Sahu DP, Singh AK, Alekhya G, Subba SH, Mishra A, et al. Adverse events following immunization of COVID-19 (Covaxin) vaccine at a tertiary care center of India. J Med Virol. 2022;94(6):2453-2459. doi: 10.1002/jmv.27655.
8. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al; 2019nCoV-302 Study Group. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021;385(13):1172-1183. doi: 10.1056/NEJMoa2107659.
9. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-1090. doi: 10.1056/NEJMoa2110475.
10. 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. doi: 10.3389/fmed.2021.760047.
11. Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, et al. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022;139(4):481-489. doi: 10.1097/AOG.0000000000004695.
12. Yonkers KA, O'Brien PM, Eriksson E. Premenstrual syndrome. Lancet. 2008;371(9619):1200-10. doi: 10.1016/S0140-6736(08)60527-9.
13. Wang YX, Arvizu M, Rich-Edwards JW, Stuart JJ, Manson JE, Missmer SA, et al. Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. BMJ. 2020;371:m3464. doi: 10.1136/bmj.m3464.
14. Male V. Menstrual changes after covid-19 vaccination. BMJ. 2021;374:n2211. doi: 10.1136/bmj.n2211.
15. Davis E, Sparzak PB. Abnormal Uterine Bleeding. [Updated 2021 Jul 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532913/
16. Yesildere Saglam H, Orsal O. Effect of exercise on premenstrual symptoms: A systematic review. Complement Ther Med. 2020;48:102272. doi: 10.1016/j.ctim.2019.102272.

17. COVID-19 Vaccines That Require 2 Shots. Centers for Disease Control and Prevention. CDC 24/7: Saving Lives, Protecting PeopleTM. Updated Dec. 17, 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/second-shot.html.
18. Dhand NK, Khatkar MS. Statulator: An online statistical calculator. Sample Size Calculator for Estimating a Single Proportion. 2014, Accessed 17 February 2022 at http://statulator.com/SampleSize/ss1P.html
19. 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. doi: 10.1177/17455057221109375.
20. 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. doi: 10.2147/IJWH.S352167.
21. 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(1):e000297. doi: 10.1136/bmjmed-2022-000297.
22. Gibson EA, Li H, Fruh V, Gabra M, Asokan G, Jukic AMZ, et al. Covid-19 vaccination and menstrual cycle length in the Apple Women's Health Study. medRxiv [Preprint]. 2022:2022.07.07.22277371. doi: 10.1101/2022.07.07.22277371. Update in: NPJ Digit Med. 2022;5(1):165.
23. Khan G, Althubaiti A, Al-Shrif A, Alsayed Z, Jifree H. Dysmenorrhea, intermenstrual bleeding, and irregularities post COVID-19 vaccination and associated factors: a retrospective observational study. Research Square; 2022. DOI: 10.21203/rs.3.rs-2218652/v1.
24. Al-Najjar MAA, Al-Alwany RR, Al-Rshoud FM, Abu-Farha RK, Zawiah M. Menstrual changes following COVID-19 infection: A cross-sectional study from Jordan and Iraq. PLoS One. 2022;17(6):e0270537. doi: 10.1371/journal.pone.0270537.
25. Lebar V, Lagana AS, Chiantera V, Kunič T, Lukanović D. The Effect of COVID-19 on the Menstrual Cycle: A Systematic Review. J Clin Med. 2022;11(13):3800. doi: 10.3390/jcm11133800.
26. Sharp GC, Fraser A, Sawyer G, Kountourides G, Easey KE, Ford G, et al. The COVID-19 pandemic and the menstrual cycle: research gaps and opportunities. Int J Epidemiol. 2022;51(3):691-700. doi: 10.1093/ije/dyab239.
27. Taşkaldıran I, Vuraloğlu E, Bozkuş Y, Turhan İyidir Ö, Nar A, Başçıl Tütüncü N. Menstrual Changes after COVID-19 Infection and COVID-19 Vaccination. Int J Clin Pract. 2022;2022:3199758. doi: 10.1155/2022/3199758.

Table 1: Socio-demographic features

Parameters	**Number (n)**	**Percentage**
AGE (YEARS)	**AGE (YEARS)**	**AGE (YEA**
>15-[?]25	1723	30.2%
>25-[?]35	2524	44.2%
>35-[?]45	1462	25.6%
MARITAL STATUS	**MARITAL STATUS**	**MARITAL**
Married	3842	67.3%
Unmarried	1858	32.5%
Separated	09	0.2%
RELIGION	**RELIGION**	**RELIGION**
Hindu	5017	87.9%
Muslim	303	5.3%
Christian	307	5.4%
Sikh	10	0.2%
Others	72	1.3%
EDUCATION	**EDUCATION**	**EDUCATI**
Postgraduate	731	12.8%

Parameters	Number (n)	Percentage
Graduate	1976	34.6%
Higher Secondary	1485	26.0%
High school	928	16.3%
Middle school	314	5.5%
Less than Middle school	101	1.8%
Illiterate	174	3.0%
OCCUPATION	**OCCUPATION**	**OCCUPAT**
Profession	953	16.7%
Semi-profession	273	4.8%
Skilled	285	5.0%
Semi-skilled	886	15.5%
Unskilled	914	16.0%
Unemployed	2398	42.0%
SOCIO-ECONOMIC STATUS	**SOCIO-ECONOMIC STATUS**	**SOCIO-EC**
Upper	97	1.7%
Upper Middle	1196	20.9%
Upper Lower	878	15.4%
Lower Middle	3179	55.7%
Lower	359	6.3%
AGE AT MENARCHE (YEARS)	**AGE AT MENARCHE (YEARS)**	**AGE AT M**
10-[?]12	1517	26.6%
13-[?]15	4192	73.4%
PARITY	**PARITY**	**PARITY**
0	3024	53.0%
1	837	14.7%
2	1415	24.8%
>2	433	7.6%
CONTRACEPTION	**CONTRACEPTION**	**CONTRAC**
Yes	632	11.1%
No	5077	88.9%
If yes then Type	If yes then Type	If yes then T
Barrier	346	54.7%
Permanent sterilization	286	45.3%
TYPE OF COVID-19 VACCINE RECEIVED	**TYPE OF COVID-19 VACCINE RECEIVED**	**TYPE OF**
COVISHIELD	4464	78.2%
COVAXIN	1245	21.8%
BOOSTER DOSE RECEIVED	**BOOSTER DOSE RECEIVED**	**BOOSTER**
Yes	833	14.6%
No	4876	85.4%
HEIGHT (m)	**HEIGHT (m)**	**HEIGHT (**
120-[?]140	82	1.4%
>140-[?]160	4525	79.3%
>160-[?]180	1102	19.3%
WEIGHT (Kg)	**WEIGHT (Kg)**	**WEIGHT**
30-[?]50	1524	26.7%
>50-[?]70	3766	65.9%
>70-[?]90	419	7.3%
BODY MASS INDEX (Kg/m^2)	**BODY MASS INDEX (Kg/m^2)**	**BODY MA**
<18.5	585	10.2%
18.5-24.9	3200	56.1%

Parameters	Number (n)	Percentage
25.0-29.9	1473	25.8%?>?
30.0	451	7.9%

Table 2: Comparison of menstrual cycle details and associated pre- and post-menstrual symptoms in women who received COVISHIELD and COVAXIN vaccines.

Parameters
AGE GROUP (YEARS)
15-[?]25
>25-[?]35
>35-[?]45
PRE-VACCINATION MENSTRUAL CYCLE DETAILS
REGULARITY OF CYCLE
Regular (28-30 days)
Irregular
DURATION OF BLEEDING (DAYS)
5 days
>5-[?]7 days
POST-VACCINATION MENSTRUAL CYCLE DETAILS IRREGULAR CYCLES
REGULARITY OF CYCLE
Regular
Irregular
DURATION OF BLEEDING (DAYS)
5 days
>5-[?]7 days
>7-[?]10 days
>10-[?]15 days
>15 days
CHANGE IN AMOUNT OF BLEEDING
Yes
No
If yes then,
Excessive
Scanty
Amenorrhea (3-5 months)
NUMBER OF PADS/DAYS
0-2
3-4
5-6
7-8
NEW ONSET PASSAGE OF CLOTS DURING BLEEDING
Yes
No
CURRENT MENSTRUAL CYCLE LENGTH
28-30 days
<20 days
>38 days
Intermenstrual bleeding

Parameters
NEW ONSET/WORSENING OF MENSTRUAL SYMPTOMS BEFORE, DURING, OR AFTER THE MI
Yes
No
If yes, then the symptoms
Severe Dysmenorrhea
Dysmenorrhea + Diarrhea
Severe lower backache
Lower Abdominal pain
Generalized weakness and body aches
Vaginal pain
Excessive white discharge
Others

Table 3: COVID-19 infection and associated changes in the menstrual cycle and pre- and post-menstrual symptoms in women who received COVISHIELD and COVAXIN vaccines.

Parameter	**COVID-19 Infection** **Before vaccination** (n=326)	**COVID-19 Infection** **During vaccination** (n=83)	**COVID-19 Infection** **After completion of vaccination** (n=307)	**COVID-19 Infection** **During and after vaccination (Twice infected)** (n=05)	**Total**	**Chi-square value**	**p-value**
VACCINE TYPE	**VACCINE TYPE**						
COVISHIELD	261(80.1%)	73(88.0%)	245(79.8%)	05(100.0%)	584	4.25	0.236
COVAXIN	65(19.9%)	10(12.0%)	62(20.2%)	0(0%)	137		
TYPE OF INFECTION	**TYPE OF INFECTION**	**TYPE OF INFECTION**	**TYPE OF INFECTION**	**TYPE OF INFECTION**	**TYPE OF INFECTION**	**TYPE OF INFECTION**	**TYPE OF INFECTION**
Mild	253(77.6%)	64(77.1%)	220(71.7%)	05(100.0%)	542	7.11	0.311
Moderate	64(19.6%)	17(20.5%)	82(26.7%)	0(0%)	163		
Severe	09(2.8%)	02(2.4%)	05(1.6%)	0(0%)	16		
NEED FOR HOSPITALIZATION	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**	**NEED FOR HOSPITALIZATION**
Yes	25(7.7%)	07(8.4%)	12(3.9%)	0(0%)	44	5.09	1.666
No	301(92.3%)	76(91.6%)	295(96.1%)	05(100%)	677		

Parameter	COVID-19 Infection	COVID-19 Infection	COVID-19 Infection	COVID-19 Infection	Total	Chi-square value	p-value
POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**	**POST-INFECTION ANY CHANGES IN THE MEN-STRUAL CYCLE**
Yes	16(4.9%)	03(3.6%)	28(9.1%)	0(0%)	47	6.296	0.098
No	310(95.1%)	80(96.4%)	279(90.9%)	05(100.0%)	674		
If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING	If yes, then CHANGES IN THE AMOUNT OF BLEEDING
Excessive	03(17.6%)	0(0%)	14(82.4%)	0(0%)	17	2.252	0.324
Scanty	01(12.5%)	01(12.5%)	06(75.0%)	0(0%)	08		
FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE	FREQUENCY OF CYCLE
<20 days (Frequent)	08(57.1%)	0(0%)	06(42.9%)	0(0%)	14	3.994	0.135
>38 days (Prolonged)	04(50.0%)	02(25.0%)	02(25.0%)	0(0%)	08		
NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES	NEW ONSET PASSAGE OF CLOTS DURING MENSES
Yes	04(21.1%)	01(5.3%)	14(73.6%)	0(0%)	19	2.709	0.258
No	12(42.9%)	02(7.1%)	14(50.0%)	0(0%)	28		
NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS	NEW ONSET PRE- OR POST-MENSTRUAL SYMPTOMS

Parameter	COVID-19 Infection	COVID-19 Infection	COVID-19 Infection	COVID-19 Infection	Total	Chi-square value	p-value
Yes 1. Severe Dysmenorrhea 2. Premenstrual burning sensation in the vagina	02(0.6%) 02(20.0%) 0(0%)	01(1.2%) 01(10.0%) 0(0%)	12(3.9%) 07(70.0%) 05(100.0%)	0(0%) 0(0%) 0(0%)	15 10 05	8.900	0.031
No	324(99.4%)	82(98.8%)	295(96.1%)	05(100.0%)	706		

Legends

Figure 1: Comparison of mean duration of bleeding pre- and post-vaccination in COVAXIN and COVISHILED groups.