

Effects of COVID-19 Vaccination on Menstrual Cycle Disturbance in Female Population

Madhuri Gupta¹, Neelam Singhal², Neha Dobriyal³, Kambhampati Darshitha⁴

¹Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India
Email: madhurijaiswal71[at]ymail.com

²Ideal Institute of Technology, College in Ghaziabad, Uttar Pradesh
Email: jaiswalneelam5[at]gmail.com

³Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India
Email: ndobriyal10[at]gmail.com

⁴Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India
Email: darshithakambhampati[at]gmail.com

Abstract: *The COVID-19 widespread situation had caused most of the females to face the issues related to delay in menstrual cycle for weeks or months. The menstrual cycle frequency had been very seriously affected due to post-vaccination changes in females such as rate of flow, cycle duration, discomforts etc. After pandemic the emotional and physical stress levels of an individual brought changes in lifestyle and SARS-CoV-2 infection is an additional factor that affected the menstruation. SARS-CoV-2 virus weakens the immune system and imbalances the psychological stress that had effects on the disturbance of menstruation cycle which resulted in inflammatory and immunological reactions during menstruation cycle. Irregular menstruation cycle causes infertility in women. There are many factors that affects mensuration cycle are obesity, anovulatory cycles, amenorrhea, oligomenorrhea, polycystic ovary syndrome, thyroid disease, viral disease, medication and vaccination. During the pandemic, a number of pharmaceutical companies, including Bharat Biotech (BB), Serum Institute of India (SII) and Dr. Reddy's laboratories started clinical studies for the vaccines such as Covaxin, Covishield, and Sputnik V. The first dose of SARS-CoV-2 is weaker as immunological factor in human beings and the SARS-CoV-2 vaccine second dose had stronger immunological factor in humans. The most frequent changes included shorter and longer menstrual cycles as well as heavier than normal menstruation. This high-quality research could have implication for society after post Covid-19 vaccination. After COVID-19 immunization, several investigations also aim to elucidate the processes behind the potential effects of COVID-19 vaccines on the menstrual cycle.*

Keywords: Menstruation cycle, Vaccine, Covid-19, Menstrual abnormalities, Hormones

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Syndrome-Coronavirus-2 (SARS-CoV-2). The first known case was identified in Wuhan city (China) in December 2019. The COVID-19 symptoms are variable but often include fever, fatigue, cough, breathing difficulties, loss of smell and taste. This disease quickly spread worldwide within 11 March 2020, World Health Organization (WHO) declared the novel COVID-19 outbreak to be a global pandemic (1). All nations were urged to act swiftly and forcefully to stop the disease's spread. A task force was formed in April 2020 to conduct focused research on the COVID-19 vaccine, with the goal of advancing vaccine development. A wide range of vaccine related adverse effects were documented in numerous trials that cover minor symptoms like fever, chills, headache, exhaustion, and arm pain to serious side effects like anaphylaxis and thrombosis (2). Other preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, use of face masks or coverings in public, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face (3).

Menstrual cycle disease

The menstrual cycle is monthly set of changes that a woman's body undergoes in preparation for pregnancy. The average gap between the menstrual cycle is 28 days (4). It can

sometimes be a bit shorter or longer. A woman's periods are irregular if the gap between them is < 21 days or more than 35 days. Menstrual irregularities can have a variety of causes, including obesity, hormonal imbalances, anovulatory cycles, amenorrhea, oligomenorrhea, polycystic ovary syndrome, thyroid disease, viral disease (5). There are many other factors that effects i. e. infections, certain medication and vaccination (6). The reported prevalence of of mensuration cycle length disorder i. e. dysmenorrhea varies among various countries, ranging from 50% to 90% (7). In India this varies from 5% to 35% among 18-30 years old women depending on their age, occupation and state (8).

COVID-19 vaccines

The COVID-19 epidemic caused stress in the world's population influencing people's lifestyles. During the pandemic, a number of pharmaceutical companies, including Bharat Biotech (BB), Serum Institute of India (SII) and Dr. Reddy's laboratories started clinical studies for the vaccines such as Covaxin, Covishield, and Sputnik V. Serum Institute of India and Bharat Biotech, an Indian company, manufactured the two COVID-19 vaccines i. e. COVISHIELD and COVAXIN (9) other than these vaccines Sputnik V, Moderna, Pfizer, Oxford-Astrazeneca, Novavax, Johnson & Johnson, Zydus Cadila's, and Coronavac vaccines are primarily utilized in other nations (10). The first dose of SARS-CoV-2 is weaker as immunological factor in human

Volume 13 Issue 7, July 2024

Fully Refereed | Open Access | Double Blind Peer Reviewed Journal

www.ijsr.net

beings and the but second dose had stronger immunological factor in humans.

COVAXIN, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV). COVISHIELD vaccine manufactured with the partnership of Pune-based Serum Institute of India Pvt Ltd, with the help of Oxford University. Russian Direct Investment Fund (RDIF) and Serum Institute of India, the world's largest vaccine manufacturer by volume, to start production of Sputnik vaccine in September 2020 (11).

Moderna Inc has collaborated with the US National Institute of Health (NIH) for conducting their mRNA-based vaccine. Pfizer-BioNTech COVID-19 vaccine has not been approved

or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent COVID2019. The Oxford–AstraZeneca COVID-19 vaccine, sold under the brand names Covishield and Vaxzervria among others, is a viral vector vaccine for the prevention (12). AstraZeneca takes responsibility for the safety, effectiveness and quality of all the COVID-19 vaccine made in our global supply network of manufacturing facilities across Europe, North, Central and South America, Asia and Australia. The Janssen COVID-19 vaccine, sold under the brand name Jcovden, is a COVID-19 vaccine that was developed by Janssen Vaccines in Leiden, Netherlands. ZyCoV-D is a DNA plasmid-based COVID-19 vaccine developed by Indian pharmaceutical company Cadila Healthcare, with support from the Biotechnology Industry. Some of common vaccines its types and manufacture are as:

S. No	Vaccine name	Type of vaccine	Manufacturer
1	Covishield	Viral Vector	Oxford University & Astra Zeneca
2	Covaxin	Inactivated virus	Bharat Biotech
3	Sputnik V	Recombinant Viral Vector (human rAd26 and rAd5 vector)	Dr Reddy's in India (RDIF) & Gamaleya Research Institute
4	Moderna	mRNA	Moderna
5	Pfizer	RNA (S protein (Spike protein))	Pfizer & BioNTech
6	Oxford-AstraZeneca	Viral Vector	Oxford Uni AstraZeneca
7	Novavax	Protein Based	Novavax & Serum India
8	Janssen	Viral Vector	Johnson & Johnson & Biological E (BioNTech)
9	ZyCov-D	DNA	Zydus Cadila
10	CoronaVac	Inactivated Virus	Sinovac

Effect of COVID-19 Vaccination on Menstrual Cycle

A woman's menstrual cycle is regulated by endocrine, autocrine, and paracrine hormones that affect ovarian follicular development, ovulation, luteinization, luteolysis, and endometrial remodelling (13). The menstrual cycle is impacted by reproductive endocrine disorders, which include anovulatory cycles, irregular menstrual periods, amenorrhea, oligomenorrhea, and polycystic ovarian syndrome. Progesterone and oestrogen levels are low on the first day of menstruation, but luteinizing and oestrogen hormones rise from 12–14 days after ovulation. Subsequently, progesterone levels are marginally normal and oestrogen and luteinizing hormone levels fall (14).

A recent study found that receiving the COVID-19 immunization caused a number of mensuration problems, including longer cycles, pain, and bleeding. As a mechanism for the biological link between COVID-19 vaccination and menstrual abnormalities, the systemic immune response after vaccination might interfere in many pathways that are involved in the menstrual cycle as shown in fig 1, 2 (15).

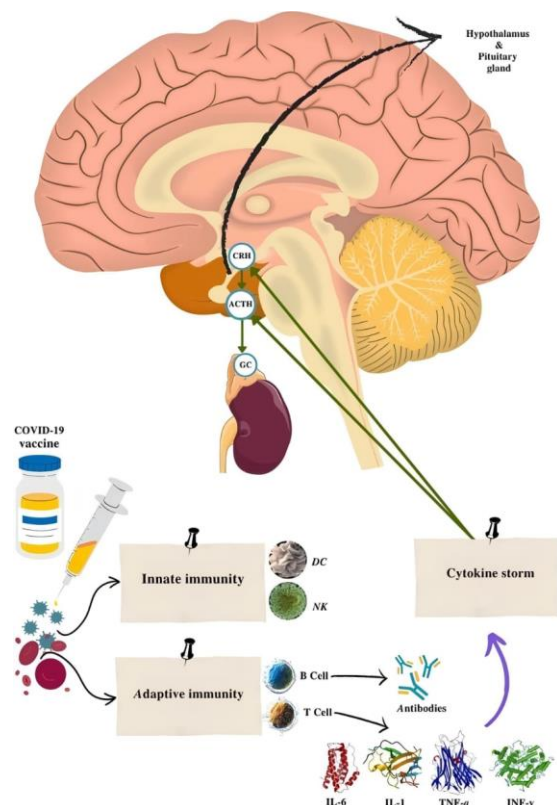


Figure 1: The effects of COVID-19 vaccines on the immune pathways

Green arrows depict the stimulatory effects. ACTH: adrenocorticotrophic hormone, CRH: corticotrophin-releasing hormone, DC: dendritic cell, GC: glucocorticoid, IL-1: interleukine-1, IL-6: interleukine6, INF-γ: interferone-γ, NK: natural killer cell, TNF-α: tumor necrosis factor-α.

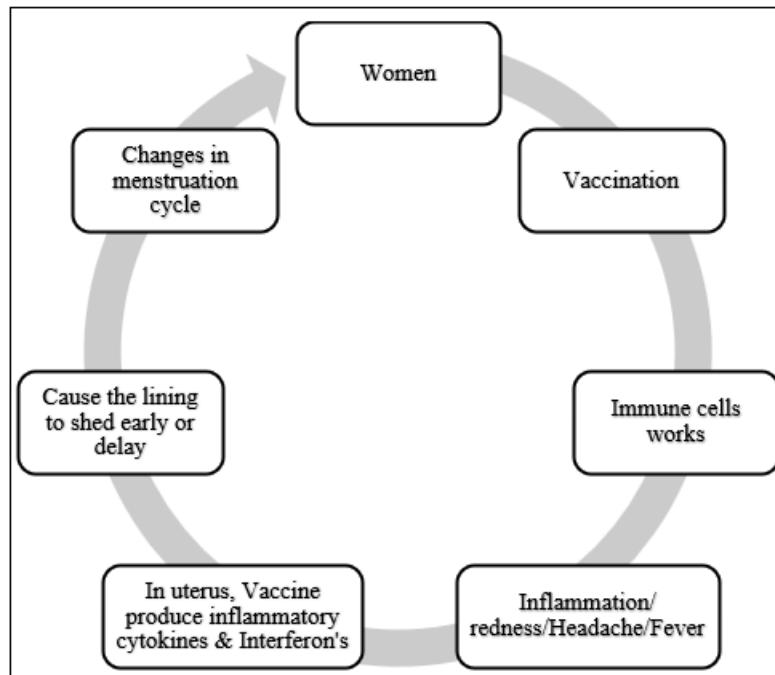


Figure 2: The effects of COVID-19 vaccines on the immune pathways

International and National status of COVID-19 vaccine on menstruation cycle

COVID-19 vaccination may be associated with change in menstrual cycle length. A statistical data of different countries is shown in the following way:

United States of America: In an American experimental study, it was found that the first immunization dosage had no effect on the timing of subsequent periods, whereas the second dose was associated with a 0.45-day delay with consecutive interval of 2.32day, who received both vaccine doses (16). In another study named the “Apple Women’s Health Study”, a longitudinal mobile-application-based cohort study on people in the U. S. with manually logged menstrual cycles 55% of vaccinated participants received Pfizer-BioNTech’s mRNA vaccine, 37% received Moderna’s mRNA vaccine, and 8% received the Johnson & Johnson/Janssen vaccine. This study shows that COVID-19 vaccination was associated with a small increase in their menstrual cycles in which participants received the first dose (0.50 days) and second dose (0.39 days) compared with pre-vaccination cycles (17).

A global, retrospective cohort study was done in US and Canada, 19 622 participants (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). Most people from the UK (n=6222; 31.71%), US and Canada (28.59%), and Europe (33.55%), received the Pfizer-BioNTech COVID-19 vaccine. 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 0.71day for first dose and 0.56day increase for second dose. The adjusted difference was larger in people who received two doses in a cycle i. e.3.70 days. This study shows that changes in Menstruation

cycle length was less affected by vaccination in United States of America (18).

United Kingdom: In the United Kingdom, the Medicine and Healthcare Products Regulatory Agency (MHRA) has recorded, as of their update on 17 November 2021, total no of incidents of 41, 919 menstrual issues were reported, which shows heavier bleeding than usual cycles, delayed periods and unexpected vaginal bleeding (19).

Middle East: Menstrual abnormalities were detected in 66.8% of individuals in the Middle-East, Jordan. Irregular menstruation was reported by 67.5 of those who had a proven history of COVID-19 infection. Medication from Pfizer-BioNTech, Sinopharm, and AstraZeneca was administered to the majority of individuals (48.4%, 35.3%, and 13.4%, respectively) (20).

Saudi Arabia: In the Norwegian Young Adult Cohort study, the prevalence of any menstrual disturbance was 37.8% before immunization.0.98 % of Pfizer BioNTech shots and 0.68 % of ChAdOx1 immunizations had vaccinated. The relative risk of experiencing heavier bleeding than usual during the exposed versus unexposed period was 1.90 (or 95% in the case of the first vaccine dosage) and 1.84 (or 54% in the case of the second vaccine dose) (21).

Changes in menstrual cycle characteristics after COVID-19 vaccination among women in Saudi Arabia were reported by 54.7% of respondents. The most common change was in cycle length, followed by the number of menstruation days and bleeding flow. This study shows that menstrual changes were not associated with age, BMI, occupation, marital status, or medical history. Changes in intermenstrual bleeding were more frequently reported after the third dose of the Pfizer vaccine compared to the Moderna vaccine (22).

Bing Zang: According to Bing Zang (a Chinese website), 13, 118 out of 14, 431 cases of menstrual issues found in the

survey were connected to the COVID-19 immunization. 9613 cases (73.28%) were immunized by Pfizer-Biotech, 2748 cases (20.95%) were immunized by Moderna, and 742 cases (5.66%) by Janssen. Women in the 30 to 49 years old age group experienced menstrual irregularities at a higher rate (42.55%) (23).

Italy: In a study, Italy was observed that female recipients of the vaccines Janssen (Johnson & Johnson), Spikevax (Moderna), Comirnaty (Pfizer-BioNTech), and Vaxzevria (AstraZeneca) reported variations in the frequency of their subsequent menstrual cycles, as did 66.7 % of Vaxzevria recipients, 57.1 % of Comirnaty recipients, and 47.4 % of Spikevax recipients. Two-thirds of the 94 women who experienced irregular menstrual cycles after the first dose did so only in the first month, 5% only in the second, 19% only in the first and second, and 44.7% only for longer than two months (24).

India: Numerous scientific surveys have been conducted in India, provide growing proof that the COVID-19 immunization may affect people's menstrual cycles. A cross-sectional study, 773 university students of Delhi University participated, with a mean age of 20.6 ± 1.7 years, were who had received either partial or full vaccination against SARS-CoV-2. Data was gathered through a questionnaire designed to assess the relationship between menstrual changes and the SARS-CoV-2 vaccination. The participants reported a significant increase in the irregularity of the menstrual cycle with slight increase in the length of the menstrual cycle, from 30.0 ± 4.0 days (pre-vaccination) to 30.5 ± 5.6 days (post-vaccination), which was statistically significant p significant ($p < 0.001$). The duration of menstruation also increased, from 4.9 ± 1.7 days (pre-vaccination) to 5.0 ± 1.7 days (post-vaccination). However, this increase in menstrual length due to vaccination was not statistically significant ($p = 0.898$). Notably, there was a significant increase in pain reported by the participants after receiving the SARS-CoV-2 vaccine i. e. Covishield and Covaxin ($p = 0.004$) (25).

In another study, multi-centric observational study conducted in six institutes of national importance in different states of India over one year. A total of 5709 female participants fulfilling the criteria were enrolled. Data about the impact of vaccines (Covishield and Covaxin) and prior COVID-19 infection on the menstrual cycle and its associated symptoms were obtained using all participants' online and offline interviews. Out of 5709 participants, 78.2% received Covishield and 21.8% Covaxin. Of the total 5709 participants, (5.8%) developed post-vaccination menstrual disturbances, with 32.7% having frequent cycles, 63.7% prolonged cycles, and 3.6% inter-menstrual bleeding. A total of 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 the menstrual cycle ($p=0.011$) and length (0.001) were significantly higher in the Covaxin group (7.2%) as compared to the Covishield (5.3%) group. A total of 721 participants complained of newly developed/worsening pre and post-menstrual symptoms. These symptoms were significantly higher in The Covishield group ($p=0.031$), with generalized weakness and body pains as the main complaints ($p=0.001$). No significant difference was observed in the incidence of

COVID-19 infection with these vaccines. No significant associations were observed during the comparison of menstrual abnormalities among those with COVID-19 infection ($p > 0.05$) with 94.7% having no change in the amount of bleeding during menstruation post-vaccination. The menstrual irregularities observed were significantly higher with the Covaxin vaccine. Others: Further, long-term studies are required to confirm that the impact of COVID-19 vaccination on the menstrual cycle may be short-lasting, with no severe effects on women's menstrual health (26).

2. Discussion

In general, menstrual irregularities were widespread independent of immunization. After vaccination it has been observed a statistically significant increase in menstrual disruptions, especially in cases of heavier than usual bleeding, longer length, and shorter intervals between menstruations. The mechanisms behind these results could include endocrine changes and general bleeding disorders along with many other factors including stress which can momentarily modify the menstrual cycle and is governed by complex interactions between the body's tissues, cells, and hormones (3). Menstruation was also impacted by stress related to the pandemic, lifestyle modifications brought on by the outbreak, and infection with SARS-CoV-2. These careful scientific studies will increase our awareness of the potential effects of COVID-19 immunizations on menstruation by educating menstrual women. Immunological responses to a COVID-19 immunization affected the interplay between immune cells and signals in the uterus, potentially leading to small changes in the menstrual cycle (5).

3. Conclusion

Disturbance in menstrual cycle is an adverse reaction of COVID-19 vaccine. Menstruation cycle that effected female population was found to be 29.30%, 45.55%, 47.40% 37.80% and 66.80 % in America, Bing Zang, Italy, Norway and middle East Asia. In addition, some people may have experienced temporary changes in their menstrual flow or menstrual cycles due to the coronavirus infection. The most commonly observed changes are shorter than normal periods and longer menstrual cycles. However, these changes are usually minor and tend to return to normal with two to three consecutive menstrual cycles. Hence, the menstrual cycle was definitely affected by coronavirus vaccination but do not have prolong side effects.

4. Future Scope

Further research can be carried out on this topic based on the COVID-19 vaccination effect on pregnant women especially during their gestation period. Their oestrogen and progesterone hormone levels changes can be examined during this period. Awareness about the side effects of the vaccination can be given to the women especially those who live in rural places.

References

- [1] Al-Kuraishy, H. M., Al-Gareeb, A. I., Faidah, H., Al-Maiah, T. J., Cruz-Martins, N., & Batiha, G. E. S. (2021). The looming effects of estrogen in Covid-19: a rocky rollout. *Frontiers in Nutrition*, 8, 649128.
- [2] Purohit, N., Chugh, Y., Bahuguna, P., & Prinja, S. (2022). COVID-19 management: The vaccination drive in India. *Health Policy and Technology*, 11 (2), 100636.
- [3] Begum, M., Das, S., & Sharma, H. K. (2016). Menstrual disorders: causes and natural remedies. *J Pharm Chem Biol Sci*, 4 (2), 307-20.
- [4] Baloch, S., Baloch, M. A., Zheng, T., & Pei, X. (2020). The coronavirus disease 2019 (COVID-19) pandemic. *The Tohoku journal of experimental medicine*, 250 (4), 271-278.
- [5] Hause, A. M. (2021). COVID-19 vaccine safety in adolescents aged 12–17 years—United States, December 14, 2020–July 16, 2021. *MMWR. Morbidity and mortality weekly report*, 70.
- [6] Reed, B. G., & Carr, B. R. (2015). The normal menstrual cycle and the control of ovulation.
- [7] Quint, E. H. (2008). Menstrual issues in adolescents with physical and developmental disabilities. *Annals of the New York Academy of Sciences*, 1135 (1), 230-236.
- [8] Holesh, J. E., Bass, A. N., & Lord, M. (2017). Physiology, ovulation.
- [9] Diez-Buil, H., Hernandez-Lucas, P., Leirós-Rodríguez, R., & Echeverría-García, O. (2024). Effects of the combination of exercise and education in the treatment of low back and/or pelvic pain in pregnant women: systematic review and meta-analysis. *International Journal of Gynecology & Obstetrics*, 164 (3), 811-822.
- [10] Trogstad, L. (2022). Increased occurrence of menstrual disturbances in 18-to 30-year-old women after COVID-19 vaccination. Available at SSRN 3998180.
- [11] Male, V. (2021). Menstrual changes after covid-19 vaccination. *Bmj*, 374.
- [12] Patel, V., & Patel, K. (2021). Study of Awareness Regarding Covid-19 Vaccines Among General Population.
- [13] Eunice Kennedy Shriver National Institute of Child Health and Human Development. Item of interest: NIH funds studies to assess potential effects of COVID-19 vaccination on menstruation.2021. <https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation>
- [14] World Health Organization. (2020). Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020 (No. WHO/COVID-19/laboratory/2020.4). World Health Organization.
- [15] Mansour, F. R., Keyvanfar, A., Najafiarab, H., Firouzabadi, S. R., Sefidgar, S., Chayijan, S. H., . . . & Tehrani, S. (2023). Menstrual disturbances following COVID-19 vaccination: A probable puzzle about the role of endocrine and immune pathways. *Journal of Reproductive Immunology*, 103952.
- [16] Von Woon, E., & Male, V. (2022). Effect of COVID-19 vaccination on menstrual periods in a prospectively recruited cohort. *medRxiv*, 2022-03.
- [17] Cohort, A. U. S. (2022). Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination. *Obstet Gynecol*, 139, 1-9.
- [18] Nguyen, B. T., Pang, R. D., Nelson, A. L., Pearson, J. T., Benhar Noccioli, E., Reissner, H. R., . . . & Acuna, J. (2021). Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. *PLoS One*, 16 (10), e0258314.
- [19] Muhaidat, N., Alshrouf, M. A., Azzam, M. I., Karam, A. M., Al-Nazer, M. W., & Al-Ani, A. (2022). Menstrual symptoms after COVID-19 vaccine: a cross-sectional investigation in the MENA region. *International journal of women's health*, 395-404.
- [20] Gibson, E. A., Li, H., Fruh, V., Gabra, M., Asokan, G., Jukic, A. M. Z., . . . & Mahalingaiah, S. (2022). Covid-19 vaccination and menstrual cycle length in the Apple Women's Health Study. *npj Digital Medicine*, 5 (1), 165.
- [21] Fallatah, N. I., Alrehaili, B. O., Alsulami, S. S., & Al-Zalabani, A. H. (2024). Menstrual Changes Following COVID-19 Vaccination: A Cross-Sectional Study. *Medicina*, 60 (2), 206.
- [22] Edelman, A., Boniface, E. R., Benhar, E., Han, L., Matteson, K. A., Favaro, C., . . . & Darney, B. G. (2022). Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a US cohort. *Obstetrics & Gynecology*, 139 (4), 481-489.
- [23] Zhang, B., Yu, X., Liu, J., Liu, J., & Liu, P. (2022). COVID-19 vaccine and menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System (VAERS). *BMC Women's Health*, 22 (1), 403.
- [24] Laganà, A. S., Veronesi, G., Ghezzi, F., Ferrario, M. M., Cromi, A., Bizzarri, M., . . . & Cosentino, M. (2022). Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey. *Open Medicine*, 17 (1), 475-484.
- [25] Tandon, A., Kumar, N., Aggarwal, S., Anjana, Y., Sachdeva, M. P., Gupta, V., . . . & TRILOK-KUMAR, G. E. E. T. A. (2023). Assessing menstrual changes among young Indian females post-SARS-CoV-2 vaccination. *Cureus*, 15 (12).
- [26] Kumar, N., Gangane, N., Mohapatra, I., Rukadikar, C., Sharmila, V., Pushpalatha, K., . . . & Negi, K. (2023). " Effect of COVID-19 Vaccination on Menstrual Cycle Patterns of Reproductive-Age Women: A Multi-centric Observational Study. ". *Current Drug Research Reviews*.

Author Profile



Dr. Madhuri Gupta, working as Scientist in National Poison Information Centre, Deptt. of Pharmacology, AIIMS, New Delhi from last fifteen years. I have done my M. Sc. and Ph. D. in Chemistry from Gorakhpur University, Uttar Pradesh. I have also worked in Indian Institute of Science, Bangalore & Shriram Institute of Industrial Research, New Delhi. My co-research areas are metal toxicity in human, nano-formulations in dental materials, microbial and cell culture techniques.



Dr. Neelam Singhal, have eight years of experience in teaching in various Engineering Colleges and labs. My objective is to work in challenging atmosphere, intend to work in consistent growing technical environment together with honing my skills for the mutual development.



Neha Dobriyal is a medical technology Graduate and Master in Biochemistry. I have experience of working in the Area of microbial pathogens, oral microbiota, nanoparticles and phytochemicals of medicinal plants.



Kambhampati Darshitha, have completed my bachelors and masters in Forensic Science with a specialization in Nanotechnology. Now working in a project, funded by ICMR, AIIMS, New Delhi.